CLINICAL STUDY PROTOCOL

ARC011
Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children, Active Treatment Arm Open-Label Extension Study (RAMSES OLE)

Protocol Amendment 2.0 – 20 Aug 2018
Reference Numbers: NCT03337542

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United States

CLINICAL STUDY PROTOCOL

Protocol Title:	Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children, Active Treatment Arm Open-Label Extension Study (RAMSES OLE)
Investigational Drug:	AR101, Characterized Peanut Allergen
Protocol Number:	ARC011
IND Number:	15463
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Boulevard Suite 300 Brisbane, CA 94005 United States Telephone: +1 650-614-5220
Original Protocol:	0.0 – 01 Aug 2017
Amendments	
Global:	1.0 – 24 Jan 2018
Global:	2.0 – 20 Aug 2018

This study will be conducted according to the Declaration of Helsinki (2013), principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents, EU Directive 2001/20/EC (the Clinical Trials Regulation), EU Directive 2005/28/EC (Good Clinical Practice Directive), and local applicable legislation including but not limited to the UK SI 2004/1031 Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

CLINICAL STUDY PROTOCOL ARC011

Sponsor Personnel

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Principal Investigator Protocol Acknowledgement

Clinical Study Protocol ARC011	Global Amendment 2.0
Sponsor: Aimmune Therapeutics, Inc.	Date: 20 Aug 2018
Title: Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children, Active Treatment Arm Open–Label Extension Study (RAMSES OLE)	

I have read this Clinical Study Protocol ARC011. As the principal investigator, I agree to conduct this protocol according to Good Clinical Practice, 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 Guideline for Good Clinical Practice E6, and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, national, and international requirements.

_____

Principal Investigator (Print)

_____ _____

Principal Investigator (Signature) Date

SYNOPSIS

Title	Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children, Active Treatment Arm Open–Label Extension Study (RAMSES OLE)	
Short Title	RAMSES OLE	
Clinical Phase	3	
IND Number	IND 15463	
Sponsor	Aimmune Therapeutics, Inc.	
Number of Subjects	This study is an extension of the ARC007 (RAMSES) study for subjects who received AR101 oral immunotherapy (OIT). The number of subjects who are potentially eligible to enroll in this study is approximately 330. This is based on a target enrollment of approximately 500 subjects in ARC007 and a 2:1 AR101:Placebo randomization.	
Objectives and Endpoints	**Objectives**	**Endpoints**
	The objective of this study is to describe the 6 month safety and tolerability of maintenance dosing with AR101 300 mg once daily (QD) orally in peanut-allergic children who received AR101 and completed the ARC007 study.	• Frequency of treatment-emergent adverse events (AEs), including serious AEs, during the overall study period • Frequency of premature discontinuation of dosing due to AEs • Frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs • Proportion of chronic/recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing • Frequency of allergic hypersensitivity reactions AEs • Frequency of anaphylaxis as defined in the protocol • Frequency of use of epinephrine as a rescue medication • Frequency of reported accidental/nonaccidental ingestion of peanut and other allergenic foods and severity of any resultant reactions • Assessment of asthma control using the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) • Frequency of AEs that lead to early withdrawal
	Exploratory Secondary Objectives	**Endpoints**
	To assess immunologic changes while receiving AR101 treatment	• Change in peanut-specific and peanut component-specific serum immunoglobulin E (IgE) and immunoglobulin G subclass 4 (IgG4) • Change in peanut Skin Prick Test (SPT) mean wheal diameter
	To characterize the effect of AR101 on nasal allergy symptoms in subjects with allergic rhinitis	• Change in Total Nasal Symptom Score (TNSS)

	To evaluate quality of life in subjects receiving treatment with AR101	• Changes in food allergy related quality of life as measured by Food Allergy Quality of Life (FAQLQ) questionnaire, and the Food Allergy Independent Measure (FAIM) questionnaires
Study Design	This is a phase 3, multicenter, North American, open-label, pivotal safety extension study for those subjects who received AR101 therapy in ARC007 and completed the study. The Exit Visit procedures of ARC007 will serve as part of the Screening/Baseline Visit (Visit 1) for this study (ARC011), unless specified otherwise. Eligibility will be determined after subjects provide written informed consent (and assent if required per local regulations) for the ARC011 study. Upon successful completion of the Screening/Baseline visit, subjects will be asked to return to the clinic every 4 weeks for a total of 6 additional visits (Visits 2-7) over an approximately 6 month timeframe. Subjects will continue to dose with AR101 300 mg QD for the duration of the 6 month maintenance period, unless they need to have their dose adjusted per protocol stipulations. At the end of the maintenance period, subjects will undergo an Exit Visit (Visit 7) for this study. Procedures to be performed at each visit are listed in the Schedule of Events Table in Appendix 1. Eligible subjects who would like to continue treatment with AR101 following completion of the current study will be offered the opportunity to participate in the open-label safety study ARC008. Adverse events of interest (AEI) as described in Section 8.1.4 will be monitored and reported similarly to how they were monitored and reported in ARC007 (RAMSES). **Safety Monitoring Committee** An internal Safety Monitoring Committee (SMC) will monitor the study for safety.	
Study Duration	Each subject will continue in the study until 1 or more the following occurs: • The subject completes approximately 6 months of dosing according to protocol. • The risk/benefit profile for the subject to continue in the study is no longer favorable in the opinion of the investigator. • An early discontinuation criterion is met. • The investigator withdraws the subject from the study. • The subject withdraws consent. • The sponsor discontinues development of AR101. • The sponsor discontinues development of AR101 in the relevant participating country. After one of these events occurs, the subject will return to the clinic for the Exit Visit (Visit 7) or Early Discontinuation Visit. The end of the study is defined as the last visit by the last subject in the study.	
Investigational Product and Dispensing	The investigational product (IP), AR101 (Characterized Peanut Allergen), is in the form of peanut flour formulated with a bulking agent and a flow agent which will be packaged in a sachet containing 300 mg of peanut protein. The sachet will be emptied into an appropriate food vehicle and ingested orally once a day. Sites and subjects will be supplied with detailed instructions for preparation of the dose, the timing of the dose, and if needed dose adjustment for intolerance or missed doses. If a dose adjustment is required per protocol, AR101 capsules will be provided in prepackaged dosing wallets. Each individual wallet contains 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. AR101 must be stored refrigerated with the temperature between 2°C and 8°C.	

Inclusion Criteria	Subjects must meet all the following criteria to be eligible: 1. Prior to commencing any study related activities, the subject or parent/guardian must provide written informed consent. For minors, assent will be obtained as required by the institutional review board (IRB)/ethics committee (EC). 2. Received AR101 in study ARC007. 3. Completed the ARC007 study. 4. Use of effective birth control by sexually active female subjects of childbearing potential.
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible: 1. Developed a clinically significant change in health status during the ARC007 study which in the opinion of the investigator would make the subject unsuitable for participation in this study. 2. Receiving a prohibited medication or anticipated use of a prohibited medication [eg, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or calcium channel blockers], any monoclonal antibody, any investigational peanut immunotherapy, or any other immunomodulatory therapy. 3. Currently in the build-up phase of immunotherapy for any nonfood allergen. 4. Currently participating in any other interventional clinical study outside of the ARC007 study that was just completed. 5. Hypersensitivity to epinephrine or any of the excipients in the product. 6. Currently pregnant or breastfeeding. 7. Any other condition that, in the opinion of the Investigator, precludes participation for reasons of safety.
Study Procedures	The procedures conducted during the study visits include but are not limited to the following: • Informed consent and assent • Inclusion and exclusion criteria • Demography • Medical history • Concomitant medications • Food allergen exposure update • Vital signs • Dispensing/return of AR101 • Full or abbreviated physical examination • AE/serious adverse event (SAE) assessment • Allergic reactions • C-ACT (< 12 years) or ACT • TNSS questionnaire (instantaneous [12 hour] and reflective [2 week]) • FAQLQ (completed by subject and/or parent/guardian) and FAIM • Peak expiratory flow rate (PEFR) • Review of diary/dispense new diary • AR101 compliance monitoring • SPT • Complete blood count • Peanut-specific and peanut component-specific serum IgG4 and IgE • Urine pregnancy test for females of childbearing potential • In-clinic dosing • Postdose vital signs monitoring

	• Peanut allergy training • Pediatric Eosinophilic Esophagitis Symptom Scores Questionnaire, version 2.0 (PEESS v2.0) • Telephone follow-up • Additional blood samples for optional exploratory immunologic studies. These can be obtained with the same venipuncture as the blood draw for the immunoglobulin assay. • Optional saliva collection
Statistical Considerations	There is no sample size calculation for this study. The sample size will be determined by the number of eligible subjects who participate in the prior AR101 study ARC007. Data will be summarized using descriptive statistics. No specific hypothesis testing or comparisons are planned for this study.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Asthma Control Test
AE	Adverse event
AEI	Adverse event of interest
AR101	Characterized peanut allergen, the investigational product for study ARC011
C-ACT	Childhood Asthma Control Test
CBC	Complete blood count
CFR	Code of Federal Regulations
CODIT™	Characterized oral desensitization immunotherapy
CoFAR	Consortium of Food Allergy Research
CRC	Clinical research center
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EC	Ethics committee
eCRF	Electronic case report form
EoE	Eosinophilic esophagitis
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	Informed consent form
ICH	International Council for Harmonisation
lgE	Immunoglobulin E
lgG4	Immunoglobulin G subclass 4
IND	Investigational new drug
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
OIT	Oral immunotherapy
PEESS v2.0	Pediatric Eosinophilic Esophagitis Symptom Scores Questionnaire, version 2.0
PEFR	Peak expiratory flow rate
QD	Once daily
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SMC	Safety monitoring committee
SPT	Skin prick test
TNSS	Total Nasal Symptom Score

1 BACKGROUND AND RATIONALE

1.1 Background

Updated background information is provided in the AR101 investigator brochure.

Peanut allergy is a common and serious condition that disproportionately affects children and is associated with severe reactions, including life-threatening anaphylaxis. The prevalence of peanut allergy, like other food allergies, has been rising, and is now at high levels, affecting up to 1.5% of the population (Branum and Lukacs, 2008; Sicherer and Sampson, 2014). The current standard of care in management of peanut allergy is a peanut-avoidant diet, along with education of the subject and family in the acute management of an allergic reaction, including ready access to self-injectable epinephrine. The burden of avoidance and the constant fear of accidental exposure negatively affect the health-related quality of life (QoL) for subjects 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).

In addition, peanut-avoidant diets are complicated by the difficulty of interpreting food labels and the presence of undeclared or hidden allergens in commercially-prepared foods (Joshi et al, 2002; Altschul et al, 2001; Vierk et al, 2002). Accidental exposures are common, with up to 50 percent of food-allergic subjects having ≥ 1 allergic reaction over a 2-year period (Sicherer et al, 1998).

In early clinical studies, oral immunotherapy (OIT) for peanut allergy has demonstrated encouraging safety and efficacy results in creating a change in clinical reactivity that would protect recipients from these accidental exposures (Jones et al, 2009; Hofmann et al, 2009; Blumchen et al, 2010; Yu et al, 2012; Varshney et al, 2011; Anagnostou et al, 2014). These studies involved a period of up-dosing with increasing amounts of peanut protein, a period of maintenance therapy, and then an oral food challenge to assess desensitization. Dosing symptoms observed in these studies have included rash, wheezing, rhinorrhea, sneezing, itching, abdominal pain, nausea, vomiting, and diarrhea. Most symptoms have been mild, consistent with a transient, low-grade allergic reaction, and tended to diminish in frequency with increasing duration of treatment.

There is evidence that OIT induces a clinically meaningful level of desensitization in most subjects and may also induce favorable immunologic changes over time. Though these early studies used different doses and regimens, collectively they provided supportive evidence for the efficacy and safety of peanut OIT and served as the basis for the initiation of clinical development of AR101, a standardized OIT product manufactured to pharmaceutical-grade standards and previously tested in Aimmune's phase 2 program and ongoing phase 3 programs.

The goal of OIT with AR101 is to induce and maintain a state of desensitization to peanut protein, defined as the ability to consume a specific dose of peanut protein with no or mild symptoms. This state of desensitization, in conjunction with a peanut-avoidant diet, should be sufficient to protect a peanut-allergic individual from the adverse effects of an accidental exposure to peanuts or peanut-containing foods.

1.2 Clinical Studies of AR101

Updated background information is provided in the AR101 investigator brochure.

1.2.1 ARC001 and ARC002

ARC001 is a completed phase 2, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of OIT with AR101 in peanut-allergic children and adults 4 to 26 years of age conducted in the US. ARC001 consisted of a Screening Period with a Screening double-blind, placebo-controlled food challenge (DBPCFC), an Initial Escalation Period, an Up-dosing Period to a target dose of 300 mg once daily (QD) maintained for 2 weeks, a Maintenance Period (approximately 24 weeks), and an Exit DBPCFC. Subjects were randomized to either AR101 or placebo in a 1:1 ratio. The primary endpoint of ARC001 was the percentage of desensitization responders, defined as subjects tolerating 300 mg peanut protein (443 mg peanut protein cumulative) at the Exit DBPCFC. The intent-to-treat population comprised 55 subjects: 29 in the AR101 group and 26 in the placebo group.

ARC002 is an ongoing phase 2, multicenter, open-label, follow-on study for subjects who completed ARC001. The study consists of 2 parts. Part 1 is complete and allowed subjects who received placebo to complete up-dosing to 300 mg QD and subjects who received AR101 to continue treatment with 300 mg QD. All subjects maintained the 300 mg daily dose for 12 weeks and then underwent a DBPCFC. The subjects who completed this DBPCFC were then given the choice to continue on 300 mg/day or enter a high-dose up-dosing period to a target maximum of 2000 mg/day (Part 2). Once the individual maximum tolerated dose was reached, subjects are maintained on this dose. A total of 47 subjects enrolled in ARC002, and 40 of these subjects entered Part 2.

1.2.2 ARC003 (PALISADE) and ARC004 (PALISADE Follow-On Study)

ARC003 (PALISADE) is an ongoing phase 3, international, randomized, double-blind, placebo controlled study of the efficacy and safety of AR101 characterized oral desensitization immunotherapy (CODIT™) in peanut-allergic children and adults 4 to 55 years of age. Subjects were randomized to either AR101 or placebo in a 3:1 ratio. The study consists of a Screening Period with a Screening DBPCFC, an Initial Escalation Period, an Up-dosing Period to a target dose of 300 mg QD maintained for 2 weeks, a Maintenance Period (approximately 24 weeks), and an Exit DBPCFC. A total of 554 subjects were randomized.

ARC004 is a phase 3, open-label, international, follow-on study for subjects who completed ARC003. ARC004 is designed to evaluate the effect of extending the dosing interval from daily to every other day, twice weekly, once weekly, and finally every other week. Subjects who received AR101 during ARC003 will participate in 1 of 5 dosing regimens for a period of 28 to 84 weeks, including an Extended Maintenance Period of 24 weeks. Subjects who received placebo in ARC003 will undergo initial escalation and up-dosing to a target dose level of 300 mg QD, on which they will be maintained for the 24 week Initial Maintenance Period before undergoing a DBPCFC. Subjects who tolerate ≥ 443 mg of peanut protein at

this DBPCFC will continue into the Extended Maintenance Period. At the end of the Extended Maintenance Period, all subjects will undergo an Exit DBPCFC. Subjects who do not tolerate the nondaily dosing regimens will also be offered the opportunity to enroll in ARC008.

1.2.3 ARC007 (RAMSES) and ARC008

ARC007 is an ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled study of the safety of AR101 CODIT in peanut-allergic children ages 4 to 17 years of age conducted in the US and Canada. Approximately 500 subjects will be randomized to either AR101 or placebo in a 2:1 ratio. No DBPCFC will be conducted during the study. Subjects who are randomized to AR101 will complete the Initial Escalation and Up-dosing Periods with a target dose of 300 mg QD. After tolerating the 300 mg QD dosing and maintaining this dosing regimen for 2 weeks, subjects having received AR101 will be eligible to rollover into study ARC011 described below followed by ARC008. Subjects who received placebo in ARC007 will be eligible to rollover into ARC008 directly and undergo initial escalation and up-dosing to a target dose level of 300 mg QD.

ARC008 is a phase 3, international, multicenter, open-label, long-term safety study of AR101 in a CODIT regimen in peanut-allergic children and adults. Subjects who received placebo during ARC007 may enroll in ARC008. Additional subjects will originate from one of the following Aimmune AR101 clinical studies: ARC002, ARC004, ARC010, ARC011, or any future clinical study that identifies ARC008 as a potential poststudy option in the study protocol (the parent study).

1.2.4 ARC010 (ARTEMIS)

ARC010 is an ongoing phase 3, multicenter, double-blind, placebo-controlled study of the efficacy and safety of AR101 CODIT to be conducted in Europe. Approximately 160 peanut-allergic children ages 4 to 17 years of age will be randomized in a 3:1 ratio to either AR101 or placebo. The target dose for subjects randomized to AR101 is 300 mg QD. Subjects who reach the target dose and maintain this dose for the approximately 12-week Maintenance Period will complete a DBPCFC. Subjects who received AR101 and subjects who received placebo will be offered the opportunity to enter ARC008.

1.3 Rationale for the Current Study

ARC011 is a phase 3, pivotal, open-label extension of Study ARC007 for subjects who received AR101 during the ARC007 study. To be eligible for ARC011, a subject must have qualified for enrollment in ARC007, received active treatment with AR101 CODIT, and completed the study including the ARC007 Exit Visit. The ARC011 study will provide an additional 6 months of safety data for AR101 administered as 300 mg orally QD in subjects who were informed that they have successfully reached maintenance dosing with AR101 (in ARC007). This study is intended to assess the safety of AR101 in subjects whose behavior may be affected by their knowledge of prior treatment. Upon completion of this study,

eligible subjects will be offered the opportunity to enroll in study ARC008 and continue receiving treatment with AR101.

1.4 Known and Potential Risks and Benefits to Subjects

The current edition of the AR101 investigator brochure provides further information on the risks and benefits of AR101.

1.4.1 Risks

The risks of this study include adverse events (AEs) associated with AR101 treatment and risks of decreased vigilance in avoidance of peanut-containing foods.

1.4.1.1 Adverse Events Associated With AR101 Treatment

The most frequently reported AEs associated with AR101 treatment are mild to moderate symptoms of allergic reactions, especially those associated with the gastrointestinal (GI) tract. More specifically, AR101 CODIT has caused allergic symptoms of sneezing, rhinorrhea, urticaria, angioedema, flushing, eczema flare-ups, ocular, nasal, and oral throat pruritus, nausea, vomiting, abdominal discomfort, abdominal pain, cramping, cough, wheezing, and shortness of breath, in addition to anaphylaxis, as defined by the criteria published by the National Institutes of Allergy and Infectious Disease-Food Allergy and Anaphylaxis Network workgroup (Sampson et al, 2006).

In studies ARC001 and ARC002, the incidence of mild and moderate anaphylaxis with AR101 was 3% and 4% respectively. While these events were not graded as severe, the possibility of severe or life-threatening anaphylaxis is a potential risk of AR101 treatment.

In addition to anaphylaxis, the occurrence of eosinophilic esophagitis (EoE) is also an AE of interest. To date, there have been 2 confirmed cases of EoE in subjects treated with AR101. However, the true incidence of EoE may be underestimated because most subjects with chronic GI symptoms do not undergo endoscopy and biopsy. For example, in ARC001 and ARC002, 18% of subjects (n=6 of 55) discontinued treatment due to GI AEs, but only one of these 6 subjects underwent biopsy, and was found to have EoE. In all 6 cases, symptoms resolved within days to weeks after discontinuing therapy.

1.4.1.2 Risks of Decreased Vigilance

There may be a risk that subjects may decrease their vigilance against accidental peanut ingestion during participation in the study because they believe they are protected from it. This phenomenon has been reported in previous studies, and subjects in the study 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.

1.4.2 Benefits

There is no guarantee that subjects who participate in this study will benefit from AR101 treatment. 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.

1.4.3 AR101 Benefits and Risks Assessment

Overall, AR101 produced a high rate of desensitization to a clinically meaningful level of peanut protein in phase 2 studies, indicating that AR101 has the potential to provide treated individuals the benefit of reducing the risk of severe and life-threatening or fatal allergic reactions, which continues to justify the acceptable associated risk.

Based on the sponsor's review of all available data for AR101 OIT for peanut allergy to date, the benefit-risk profile of the product in this indication is positive.

The AR101 investigator brochure has additional information regarding the safety profile, benefits, and risks of AR101.

2 OBJECTIVES

The objectives and endpoints for ARC011 study are summarized in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
The objective of this study is to describe the 6-month safety and tolerability of maintenance dosing with AR101 300 mg once daily orally in peanut-allergic children who received AR101 and completed the ARC007 study.	• Frequency of treatment-emergent AEs, including serious AEs, during the overall study period. • Frequency of premature discontinuation of dosing due to AEs • Frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs • Proportion of chronic/recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing • Frequency of allergic hypersensitivity reactions AEs • Frequency of anaphylaxis as defined in Section 8.1.4.1 • Frequency of use of epinephrine as a rescue medication • Frequency of reported accidental/nonaccidental ingestion of peanut and other allergenic foods and severity of any resultant reactions • Assessment of asthma control using the C-ACT/ACT • Frequency of AEs that lead to early withdrawal

Objectives	Endpoints
Exploratory Secondary Objectives	**Endpoints**
To assess immunologic changes while receiving AR101 treatment	• Change in peanut-specific and peanut component-specific serum IgE and IgG4 • Change in peanut SPT mean wheal diameter
To characterize the effect of AR101 on nasal allergy symptoms in subjects with allergic rhinitis	• Change in Total Nasal Symptom Score
To evaluate quality of life in subjects receiving treatment with AR101	• Changes in food allergy related quality of life as measured by FAQLQ and the FAIM questionnaires

ACT = Asthma Control Test; AE = adverse event; C-ACT = Childhood Asthma Control Test; FAIM = Food Allergy Independent Measure questionnaires; FAQLQ = Food Allergy Quality of Life questionnaires; GI = gastrointestinal; IgE = immunoglobulin E; IgG4 = immunoglobulin G subclass 4; SPT = skin prick test.

3 STUDY DESIGN

This is a phase 3, multicenter, North American, open-label, pivotal safety extension study for those subjects who received AR101 therapy in and completed the ARC007 study. The Exit Visit of ARC007 study will serve as the Screening/Baseline Visit (Visit 1) for this study (ARC011), unless specified otherwise. Eligibility will be determined for ARC011 after the written informed consent/assent is obtained from the subject or parent/guardian.

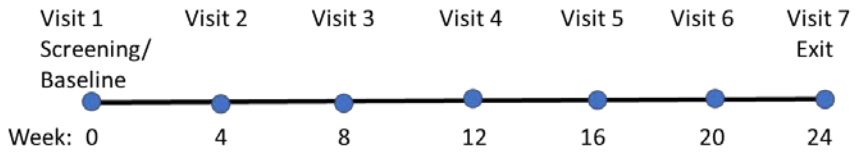
Upon successful completion of the Screening/Baseline visit, subjects will be asked to return to the clinic every 4 weeks for a total of 6 additional visits (Visits 2-7) over an approximately 6 month timeframe. Subjects will continue to dose with AR101 300 mg QD for the duration of the 6 month maintenance period unless they require a per protocol dose reduction for intolerance or missed doses. At the end of the maintenance period, subjects will undergo an Exit Visit (Visit 7) for this study. Procedures to be performed at each visit are listed in the Schedule of Events Table in Appendix 1. Eligible subjects who would like to continue treatment with AR101 following completion of the current study will be offered the opportunity to participate in the open-label safety study ARC008.

Adverse events of interest (AEI) as described in Section 8.1.4 will be monitored and reported similarly to how they were monitored and reported in ARC007 (RAMSES) study.

3.1 Study Visits

The visits shown in Figure 1 are briefly described in the sections that follow, and the details of procedures to be performed at each visit are provided in Section 7 and the Schedule of Events (Appendix 1).

Figure 1: Study Visits



Subjects who discontinue the study prior to Visit 7 will complete an Early Discontinuation Visit 2 weeks after their last dose of AR101 (See Section 4.4).

3.1.1 Screening/Baseline Visit (Visit 1)

The Exit Visit procedures of ARC007 will also serve as part of procedures for the Screening/Baseline Visit for ARC011. Potential eligible subjects and/or parents/guardians of potential eligible subjects must have signed the institutional review board (IRB)/ethics committee (EC) approved informed consent forms (ICF) and, when required by the IRB/EC, the IRB/EC approved age-appropriate subject assent prior to undergoing any ARC011 specific study procedures.

The Schedule of Events (Appendix 1) and Section 7.1 outline all procedures that will be conducted at the ARC007 Exit Visit and ARC011 Screening/Baseline visit and additionally delineates the procedures that will be conducted as part of the Exit Visit for ARC007 versus those that will be conducted solely as a part of the ARC011 Screening/Baseline Visit.

3.1.2 Maintenance Period (Visits 2-7)

Upon successful completion of the Screening/Baseline visit, subjects will be asked to return to the clinic every 4 weeks (Weeks 4, 8, 12, 16, 20 and 24; Visits 2-7) for completion of the study procedures. Visit 7 will mark the end of the maintenance period and is the study Exit Visit (see Section 3.1.4). Subjects will receive an in-clinic dose of AR101 at each clinic visit and will continue to dose with AR101 300 mg QD for the duration of the maintenance period unless dosage adjustment is required due to intolerance or missed doses. The duration of the Maintenance Period is approximately 24 weeks. For subjects that require a dose adjustment (see Section 3.1.1), the Maintenance Period may be extended to 28 weeks to allow the subject to reach and maintain the 300 mg dose prior to the Exit Visit. If a dose adjustment is required after Visit 6, the Maintenance Period may be extended beyond the 28-week time limit upon discussion with and written approval by the medical monitor. Procedures to be performed at each Maintenance Period visit are listed in Section 7.2 and in the Schedule of Events Table in Appendix 1.

3.1.3 Dose Adjustments During the Maintenance Period

Subjects who require a decrease in dose from the 300 mg dose level due to either intolerance or missed doses will down dose to a dose level as low as 120 mg or as high as 240 mg as per

the protocol recommendations in Sections 6.9.2, 6.9.3, and 6.11. Doses will be increased per Table 2 at a frequency of no less than 1 week or no greater than 4 weeks. The first dose at each dose level will be administered in the clinic as part of an Unscheduled Visit.

Subjects should continue to come to clinic on schedule for Visits 2-7 even if the subject requires a dosage adjustment.

Table 2: Dosing Adjustment Schedule

Investigational Product Dose (mg) [1]	Interval (weeks)
120	1-4
160	1-4
200	1-4
240	1-4
300	Return to every 4-week visits

[1] All mg doses shown refer to milligrams of peanut protein.

3.1.4 Exit Visit (Visit 7)

Approximately 4 weeks following completion of Visit 6 the subject will complete the maintenance period, and will undergo an Exit Visit (Week 24; Visit 7) at which time the final in-clinic dose of AR101 will be given. Procedures to be performed at the Exit Visit are listed in Section 7 and in the Schedule of Events Table in Appendix 1. Subjects who discontinue early due to chronic/recurrent GI AEs will have additional follow-up as per Section 8.1.4.2.

3.2 Safety Monitoring Committee

The Aimmune internal Safety Monitoring Committee (SMC) will monitor the study for safety. The SMC will meet at least quarterly to review the safety data generated in this clinical study in accordance with the SMC charter.

3.3 Study Design Rationale

3.3.1 AR101 Dose Regimen and Study Periods

The dose regimen in this study is predicated on the dosing regimen successfully used in the AR101 clinical development program. A 300 mg dose administered on a daily basis during the Maintenance Period has been incorporated into studies ARC002, ARC003, ARC004, ARC008, and ARC010. This dosing regimen was well tolerated in previous studies (Vickery et al, 2016; Jones et al, 2009).

3.3.2 Desensitization Measurement Procedures

Although an oral DBPCFC remains the gold standard for diagnosing peanut allergy and assessing desensitization following OIT, this procedure is time-intensive and not without risk. This study will continue to investigate the potential surrogate tests incorporated into study ARC007 (eg, peanut-specific and peanut component-specific immunoglobulin E (IgE), and peanut-specific or peanut component-specific immunoglobulin G subclass 4 (IgG_4) as potential surrogate markers of response to OIT).

3.3.3 Other Assessments

The skin prick test (SPT), safety, and immunologic assessments conducted in this study are standard procedures for desensitization studies and are those used in the Aimmune AR101 program to date. Questionnaires are used for assessment of QoL (Section 6.5), treatment satisfaction (Section 6.5), asthma control (Section 6.4) and allergic rhinitis (Section 6.4).

3.4 Number of Sites and Subjects

This study is an extension of the AR101 study ARC007 (RAMSES) for subjects who received the AR101 CODIT regimen. Investigational sites that enrolled subjects in ARC007 will have the option to participate in this study.

Based on the ARC007 study population, the number of subjects who are potentially eligible to enroll is approximately 330. This is based on a target enrollment of 500 subjects in ARC007 and a 2:1 AR101: Placebo randomization.

3.5 Study Duration and End of Study

Each subject will continue in the study until 1 or more of the following events occurs:

- The subject completes approximately 6 months of dosing according to protocol.
- The risk/benefit profile, for the subject to continue in the study, is no longer favorable in the opinion of the investigator.
- The subject meets an early discontinuation criterion.
- The investigator withdraws the subject from the study.
- The subject withdraws consent.
- The sponsor discontinues development of AR101.
- The sponsor discontinues development of AR101 in the relevant participating country.

After one of these events occurs, the subject will return to the clinic for the Exit Visit (Visit 7) or Early Discontinuation Visit. The end of the study is defined as the last visit by the last subject in the study.

4 SELECTION AND EARLY DISCONTINUATION OF SUBJECTS

4.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible:

1. Prior to commencing any study related activities, the subject or parent/guardian must provide written informed consent. For minors, assent will be obtained as age appropriate as required by the IRB/EC.
2. Received AR101 in study ARC007.
3. Completed ARC007 study.
4. Use of effective birth control by sexually active female subjects of childbearing potential.

4.2 Exclusion Criteria

A subject who meets any of the following criteria is not eligible:

1. Developed a clinically significant change in health status during the ARC007 study which in the opinion of the investigator would make the subject unsuitable for participation in this study.
2. Receiving a prohibited medication or anticipated use of a prohibited medication [eg, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or calcium channel blockers], any monoclonal antibody, any investigational peanut immunotherapy, or any other immunomodulatory therapy.
3. Currently in the build-up phase of immunotherapy for any nonfood allergen.
4. Currently participating in any other interventional clinical study outside of the ARC007 study that was just completed.
5. Hypersensitivity to epinephrine or any of the excipients in the product.
6. Currently pregnant or breastfeeding.
7. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety.

4.3 Screen Failures

A screen failure is defined as a subject who consents or a subject whose parent/guardian consents to participation in the study but does not meet the eligibility criteria.

4.4 Early Discontinuation

A subject may discontinue dosing with AR101 anytime if the investigator determines that continuation in the study is detrimental to the subject. Following early discontinuation, subjects will return to the clinic to undergo the Exit Visit.

4.4.1 Criteria for Early Discontinuation

A subject who meets any of the following must discontinue dosing with AR101:

1. Pregnancy
2. Life-threatening symptoms (Consortium of Food Allergy Research [CoFAR] grade 4; Appendix 4), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing
3. Severe allergic hypersensitivity symptoms (CoFAR grade 3; Appendix 4) that require intensive therapy (to be determined by the investigator but may include such interventions as intravenous (IV) epinephrine, intubation, or admission to an intensive care unit) or those that are recurrent. Subjects who experience severe symptoms (eg, severe nausea, rhinorrhea, or pruritus) that are not life-threatening, not requiring intensive therapy, and not associated with any other features indicating a serious clinical condition, and who the Investigator feels are suitable to continue with the study, will be discussed with the medical monitor and may continue the study under close supervision, if both the Investigator and the medical monitor deem it appropriately safe to do so.
4. Nonadherence: For subjects missing > 7 consecutive dosing days on any 1 occasion or 3 consecutive dosing days on 3 or more occasions during any part of the study other than for treatment of an AE or a dispensing error
5. Doses withheld for ≥ 15 consecutive days for recovery from acute conditions (eg, acute viral illness, bronchial hyperresponsiveness), at any point in the study.
6. Administration of 3 or more doses of epinephrine for the treatment of any single AR101-related allergic reaction

A subject who discontinues AR101 prematurely because of AEs or other safety concerns should be encouraged to continue participation by returning for the Early Discontinuation Visit. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

4.4.2 Follow-Up of Subjects Who Discontinue Treatment Early

A subject who discontinues AR101 treatment early will be followed for safety for a minimum of 14 +2 days after the last AR101 dose or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is later. The Early Discontinuation Visit will be conducted 14 to 16 days after the last AR101 dose. In addition, a subject who discontinues AR101 because of chronic or recurrent GI AEs will be followed monthly for a minimum of 6 months or until resolution or stabilization of all GI AEs (Section 8.1.4.2), whichever is longer. If the investigator becomes aware of a serious adverse event (SAE) with a suspected causal relationship to the investigational product (IP) that occurs within 14 days after the Exit Visit in a subject treated by him or her, the investigator shall, without undue delay, report the event to the sponsor.

Subjects who discontinue due to chronic/recurrent GI AEs will complete the Pediatric Eosinophilic Esophagitis Symptom Scores, version 2.0 (PEESS v2.0) questionnaire

(Franciosi et al, 2011) and return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for an in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management or the investigator deems them to be irreversible. Additional instructions for the follow-up of these subjects are provided in Section 8.1.4.2.

4.4.3 Lost to Follow-Up

A subject should only be designated as lost to follow-up if the study site personnel are unable to establish contact with the subject or parent/guardian after 3 documented attempts via 2 different methods (eg, phone, text, e-mail, certified letter). These efforts should be documented in the source documents.

4.4.4 Subject Replacement

Since this is an open-label extension study of subjects who have participated in ARC007, no subject who discontinues AR101 treatment early will be replaced.

5 STUDY TREATMENT

5.1 Formulation, Packaging, and Labeling

AR101 is characterized peanut allergen in the form of peanut flour, formulated with a bulking agent (maize starch, microcrystalline cellulose, and other excipients to prevent clumping) and a flow agent and packaged in a sachet containing 300 mg of peanut protein. Sachets will be provided in kits containing 35 individual doses.

The sachet will be emptied into an appropriate food vehicle and ingested orally once a day. Sites and subjects will be supplied with detailed instructions for preparation of the dose, the timing of the dose, and if needed dose adjustment for intolerance or missed doses.

AR101 will also be provided in capsules for subjects who require dose adjustments. Capsules containing AR101 will be provided in prepackaged dosing kits. Each individual kit will contain 21 daily doses at a given dose level, enough to supply 2 weeks of dosing plus a 7-day overage to accommodate potential visit scheduling issues.

All AR101 will be packaged and labeled at the central packaging facility. AR101 will then be shipped to a drug depot where it will be labeled and inventoried for shipment to the clinical sites. AR101 will be dispensed, according to subject identification number using a web-based interactive response system (IXRS), directly at the investigational site or the investigational site's pharmacy, according to site-specific institutional policies. AR101 will then be distributed to each subject or parent/guardian by study site personnel.

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

5.2 Preparation, Administration, and Dosing

All doses scheduled to be administered on clinic visit days will be taken at the clinic. Subjects should withhold their daily home AR101 dose on in-clinic dosing days but should take all other prescribed medications as scheduled. Doses will be administered in the clinic under the direct supervision of an appropriately qualified healthcare provider and the oversight of a physician. This dose, intended for in-clinic administration, will be removed from the dosing kit for the assigned dose level. Once a dose is removed from the 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 clinic Visits 1-6, the subject or parent/guardian will receive a kit of sachets to be taken at home. The subject or parent/guardian will be instructed to record the sachets taken at home in a diary log and to bring all unused sachets back to the clinic at the next visit. The subject or parent/guardian will be instructed to store the dosing kit in the refrigerator at all times other than when it is removed to obtain the daily dose.

In exceptional circumstances when a subject is unable to return to the clinic for the next scheduled visit (eg, travel, holidays) and continued dosing is necessary, an additional dosing kit may be dispensed on a case-by-case basis after submission of a documented request and medical monitor approval. One additional dosing kit may be dispensed to continue the current dose level if there are no safety concerns in the opinion of the investigator and medical monitor (eg, the dose level is tolerated, no intercurrent illnesses) and the subject will have access to appropriate emergency medical services as needed. Up-dosing is not allowed until the next clinic visit.

Subjects who require down dosing will be supplied with a kit of capsules (wallet) to be taken at home according to their specific dose level. Subjects will be instructed to document capsules taken at home using diary logs and to bring all unused capsules (wallet) back to the clinic at the next visit. Instructing a subject to take a partial sachet dose is not an acceptable form of dose adjustment in ARC011.

Procedures for preparation and administration of doses given in clinic or at home are the same. Dose preparation will be completed by the subject or by a supervising adult. For in-clinic dosing, dose preparation may be performed by clinic staff or by the subject or parent/guardian under the direct supervision of clinic staff for teaching and reinforcing training. The contents of the capsules or sachets will 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. AR101 may not be added to food heated above room temperature before consumption. The vehicle food must be one to which the subject is not

allergic. The volume of the vehicle food should be such that the entire AR101 dose can be consumed in a few spoonfuls. The AR101 dose should be consumed as promptly after mixing as practicable. If not consumed within 4 hours of mixing into a vehicle, the AR101-vehicle food mixture should be discarded and a new dose mixed prior to consumption. If preparing a new dose is not feasible (eg, due to limited supply), the AR101-vehicle food mixture may be stored for up to 24 hours under conditions appropriate for the vehicle food in which the AR101 was mixed. If there is a delay of more than 24 hours in consumption, this AR101-vehicle food mixture must be discarded and the process restarted with a new AR101 dose. It is recommended that each dose of AR101 be taken at a consistent time (within a 4-hour period) each day that the dose is to be taken. An interval of ≥ 8 hours should pass between doses. Per investigator judgment, a home dose may be split into 2 portions for tolerability.

The following precautions must be followed:

- Except for on days with in-clinic dosing, the daily home dose will be taken as part of a meal or heavy snack. The subject must have other food (besides the matrix vehicle) in the stomach before taking the dose.
- Dosing at the evening meal is recommended for children so the subject can be observed and supervised in the home setting by their parent(s)/guardian(s) for several hours after dosing.
- Subjects are to avoid activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths within 3 hours after dosing).
- Dosing should also not occur within 2 hours of bedtime.
- If a subject has engaged in strenuous exercise before the planned dosing time, dosing must be delayed until any signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.

Except as may be necessary during treating an AE, it is crucial that the subject takes the doses according to their assigned schedule. No attempt should be made to make up for a missed dose if greater than 6 hours have elapsed since the usual time of dosing.

5.3 Postdose Monitoring at the Clinic

All subjects will be monitored for AEs including allergic reactions following dosing in the clinic. The time period for monitoring the subject is dependent on the severity of any symptoms that occur during in-clinic dosing (Section 8).

The occurrence of any severe symptoms that include hypoxia, hypotension, change in mental status, grade 3 severe anaphylaxis (as 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 anytime must be discussed with the medical monitor, and the subject may need to discontinue dosing in the study (Section 4.4.1).

Subjects must be observed for at least 30 minutes after dosing with vital sign measurements and assessment for signs and symptoms of allergic reaction. Postdose vital signs (blood pressure, pulse rate) will be measured and signs and symptoms of allergic reaction assessed 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.

5.4 Dosing After Missed or Withheld Doses

A dose can be taken up to 6 hours after the usual time of dosing. If more than 6 hours has elapsed, the dose should not be taken and will be considered as missed.

Except as may be necessary while treating an AE, it is crucial that subjects take their doses according to their assigned schedule.

During the Maintenance Period, dosing after missed or withheld doses will occur as follows:

- **Missed 1 or 2 consecutive doses** – The next dose taken will be taken at home.
- **Miss 3 or 4 doses in a row** – The next dose would be the current dose and would be given under supervision in the clinic.
- **Miss 5-7 doses in a row** – The guidelines for Dose Adjustments during the Maintenance Period are provided in Section 3.1.3. When 5-7 consecutive doses are missed, the subject should attempt a 120 mg dose. This dose is to be administered under supervision in the clinic. 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 300 mg dose, as per Table 2. If symptoms occur, see Section 6.9.2.
- **Missed > 7 consecutive doses or 3 consecutive days of dosing on 3 occasions in the period for any reason other than treatment of an AE or a dispensing error (ie, simple nonadherence)** – Dosing will be discontinued and the subject will return for study early discontinuation.
- **Missed > 7 but < 15 consecutive doses due to an intercurrent AE** - Refer to Section 3.1.3 for options for Dose Adjustments during the Maintenance Period. All such cases should be discussed with the medical monitor prior to resumption of dosing.
- **Missed 15 or more consecutive doses for any reason** - Dosing will be discontinued and the subject will return for study early discontinuation.

5.5 Modification of Study Treatment

AR101 dose levels may be adjusted by the investigator if the subject is unable to tolerate the scheduled dose level. If such a dose modification occurs, the subject will return all unused sachets/capsules of AR101, and be dispensed capsules at the adjusted dose level. Instructing a subject to take a partial sachet dose is not an acceptable form of dose adjustment in ARC011. Specific dose adjustment procedures are discussed further in Sections 3.1.3, 6.9.3, 6.10, and 6.11.

5.6 Drug Accountability

According to Title 21 of the US Code of Federal Regulations (21 CFR §312.62) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline, the investigator is required to maintain adequate records of the disposition of IP, including the date and quantity of the drug 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 IP dispensed and returned.

All records regarding the disposition of the IP will be available for review by the clinical study monitor. Destruction of used or unused IP can occur only after the study monitor has completed drug accountability and has given approval for destruction.

5.7 Assessment of Compliance With Study Treatment and Monitoring

The subject or the subject's parent/guardian will record daily dosing and any reaction to at-home dosing and AEs occurring between clinic visits in the diary log. AR101 doses lost or destroyed at home will also be recorded in the diary log. All used and unused AR101 sachet containers and capsule wallets should be returned to the clinic at each visit for reconciliation with the study diary.

The study site personnel will provide 24-hour emergency contact information to each subject.

5.8 Treatment of Overdose

Any dose of AR101 greater than the prescribed dose within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose. The treatment should be based on any observed signs and symptoms.

In the event of an overdose, the investigator should perform the following activities:

- Contact a medical monitor as soon as possible.
- Closely monitor the participant for any AE and report as appropriate (see Section 8.2).
- Record the quantity of the excess dose as well as the duration of the overdose in the source document.
- Report the protocol deviation (see Section 13).

5.9 Concomitant Medications

Except as indicated in Section 5.9.5, all subjects may continue their usual medications during the study, including routine vaccinations and medications taken for asthma, allergic rhinitis, and atopic dermatitis. However, they must be able to discontinue antihistamines that could interfere with the assessment of an allergic reaction at least 5 half-lives prior to visits at which an SPT is conducted. Usual topical steroid use is permitted following SPT.

5.9.1 Prophylactic Medications

Although symptomatic treatment for chronic/recurrent AEs are permitted (eg, H1 or H2 histamine blockers, proton pump inhibitors, or beta-adrenergic agonists), such medications should, in general, not be routinely started in advance of symptoms; however, exceptions can be granted on a case-by-case basis following a mandatory discussion between the investigator and the medical monitor. If started, the use of these medications should be minimized and then discontinued at the earliest medically appropriate opportunity.

5.9.2 Rescue Medications

Treatment of individual acute allergic reactions during ARC011 should be according to recognized standards of care for allergy practice. In general, this could include either an antihistamine or epinephrine, along with IV fluids, a beta-adrenergic agonist (eg, albuterol), oxygen, or steroids, as indicated. Specific guidance about pharmacological and supportive treatments related to dosing reactions is provided in Section 6.11.

Subjects and parents/guardians are likely to already have an epinephrine auto-injector device, but for those who do not, an epinephrine auto-injector device will be prescribed. The expiration dates for the epinephrine auto-injectors should be tracked by the site and by the subjects or parent/guardian and resupplied as necessary. Study staff must record in each subject's medical record that the subject or parent/guardian has an unexpired epinephrine auto-injection device and has been trained in its proper usage, including injection technique.

5.9.3 Symptomatic Treatment for Chronic and/or Recurrent Adverse Events

Symptomatic treatment for chronic/recurrent AEs is permitted (except for prohibited medications [Section 5.9.5]) 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 may proceed with the symptomatic therapy in place.

5.9.4 Contraception

Subjects undergoing OIT are at increased risk for allergic reactions and may be at increased risk for anaphylaxis. Anaphylaxis can cause a dangerous drop in blood pressure and uterine contractions; 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. Oral immunotherapy, at its core, entails repeated stimulation of the immune system to affect changes in its makeup and function. The effects OIT-induced changes in the immune system might have on the course of pregnancy or fetal development are currently unknown. Accordingly, sexually active female subjects of childbearing potential are required to practice effective birth control for the duration of the current study.

Investigators must ensure that all female subjects who are postmenarchal are provided with age-appropriate counselling and information about contraception, including adequate information about the use, effectiveness, and side-effects of contraceptive methods, using sensitivity and a patient-centered approach, and in a private setting where possible.

Sexually active women of childbearing potential will be required to use one of the following types of contraception:

- A highly effective method of birth control, defined as one 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, or a vasectomized partner.
- An effective, double barrier method of contraception (eg, male condom with female condom, cervical cap, diaphragm, or contraceptive sponge).

5.9.5 Prohibited Medications

Use of the following medications is prohibited during the study:

- Use of any therapeutic antibody or any other immunomodulatory therapy
- Systemic corticosteroids used for longer than 3 consecutive weeks throughout the study (if used, subjects must not be up-dosed during the 3 days after the last dose of oral steroids)
- Oral beta-blockers
- Angiotensin-converting enzyme inhibitors
- Angiotensin-receptor blockers
- Calcium channel blockers
- Tricyclic antidepressants.

During 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 study. The use of medication with known cardiovascular side effects during the study is discouraged; however, if an

investigator deems such use necessary, it must be undertaken with caution. It is beyond the scope of this protocol to list all drugs with cardiovascular side effects. Other than those cardiovascular drugs included in the exclusion criteria, other classes of drugs with a high potential for cardiovascular side effects include antipsychotics, cyclooxygenase-2 inhibitors (chronic use), nonsteroidal 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 a medical monitor.

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 (eg, cyclosporine, tacrolimus, antitumor necrosis alpha drugs, and other anticytokine drugs). If an investigator contemplates the use of a potentially immunomodulatory drug during the study, the investigator should discuss this with a medical monitor.

6 STUDY PROCEDURES

6.1 Safety Assessments

6.1.1 Medical History/Allergy History

A complete medical and allergy history will be recorded in the source document at the Screening/Baseline Visit (Appendix 1).

6.1.2 Adverse Events

Adverse events will be evaluated with the subject at each on-site visit (Appendix 1), recorded in the source document, and updated at each visit. See Section 8 for details.

6.1.3 Concomitant Medications

Concomitant medications will be reviewed with the subject at each on-site visit (Appendix 1) recorded in the source document, and updated at each visit.

6.1.4 Food Allergen Exposure Update

Food allergen exposure will be reviewed with the subject at each on site visit (Appendix 1), recorded in the source document, and updated at each visit.

6.1.5 Physical Examination

A complete physical examination will be recorded at the Screening/Baseline Visit and at Visit 7 (or at the early discontinuation visit). Abbreviated (symptom-directed) physical examinations will be conducted at Visits 2 – 6 and at unscheduled visits as needed (Appendix 1) and the findings recorded in the source document.

Height and weight will be recorded as part of a complete physical exam.

6.1.6 Vital Signs

Vital signs (blood pressure, pulse rate, and body temperature taken predose) will be measured at each on-site visit (Appendix 1) and the measurements recorded in the source document. Measurement of blood pressure and pulse rate should be preceded by at least 5 minutes of rest for the subject.

Additional vital sign measurements will occur post dosing as per Section 5.3.

6.1.7 Complete Blood Count

Blood samples will be collected at the time points indicated in the Schedule of Events (Appendix 1) after the predose vital signs and peak expiratory flow rate (PEFR) and before administration of AR101.

Full details of the collection and shipping requirements for the samples are provided in the Central Laboratory Manual. The central laboratory will send a laboratory report to both the site and the sponsor.

6.1.8 Pregnancy Test

All sexually active females of childbearing potential will undergo a urine pregnancy test at the time points indicated in the Schedule of Events (Appendix 1) and the results recorded in the source document.

A female is considered of childbearing potential (ie, fertile, after menarche and until becoming postmenopausal) unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

6.1.9 Pediatric Eosinophilic Esophagitis Symptom Scores, Version 2.0

All subjects who discontinue dosing due to chronic/recurrent GI AEs will complete the PEESS v2.0 questionnaire (Franciosi et al, 2011) and return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management or the investigator deems them to be irreversible.

6.2 Desensitization Measurement Procedures

Desensitization assessment procedures will be conducted at the time points indicated in the Schedule of Events (Appendix 1) and recorded in the source document.

Detailed instructions for conducting these procedures are provided in the Study Procedures Manual.

6.2.1 Skin Prick Test

SPTs will be conducted at the time points indicated in the Schedule of Events (Appendix 1) and wheal measurements recorded in the source document. SPTs will be performed using procedures for food allergens approved by both the investigational site and the sponsor. At the time that the SPT is performed, the subject must not have taken antihistamines or other medications that could interfere with the assessment of the SPT for an appropriate length of time (eg, 5 half-lives of the antihistamine that is being used or other medications in question).

A SPT probe containing a commercial peanut allergen extract is pressed into the epidermis. Positive (histamine) and negative (saline-glycerin) controls are also utilized to establish that the response is not blocked and to determine if there is dermatographism, respectively.

6.3 Peanut Allergy Training

Peanut allergy training will be provided at each on site visit (Appendix 1) and the provision of training recorded in the medical notes.

Subjects and parents/guardians (as appropriate) will be instructed to continue to follow a peanut-avoidant diet.

Subjects and parents/guardians (as appropriate) will also receive training about food/peanut allergy according to the investigational site's established standards. This training will 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)
- Investigators will train all subjects to adhere to a strict poststudy peanut elimination diet at the Exit or Early Discontinuation Visit

6.4 Asthma and Allergic Rhinitis Assessments

6.4.1 Peak Expiratory Flow Rate

For subjects ≥ 6 years of age, obtain PEFR at approximately the same time of day for each assessment visit (eg, morning, afternoon); record the best result of 3 attempts at the time points indicated in the Schedule of Events (Appendix 1). If PEFR shows a clinically relevant reduction or clinical deterioration (eg, active wheeze on physical examination) or as clinically indicated on unscheduled visits, obtain spirometry (FEV_1); record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment).

6.4.2 Asthma Control Test and the Childhood Asthma Control Test Questionnaire (for Subjects With Known Asthma Only)

The Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT) will be administered only to subjects with known asthma during each visit and prior to the measurement of lung function (Appendix 1). Results will be recorded in the source document.

The ACT (Schatz et al, 2006) is a self-administered 5-item questionnaire for subjects 12 years of age or older. It assesses the level of asthma control during the prior 4 weeks. Specifically, the test asks about shortness of breath, general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and the overall self-assessment of asthma control. Each question is scored with a 5 point scale, with lower numbers equating to worse control. The scores for each question are totaled, and a composite score of more than 19 indicates well-controlled asthma. Subjects who have turned 12 since entry into the ARC007 study will be asked to complete the ACT.

The C-ACT (Liu et al, 2007) is a 7 item questionnaire for subjects aged 4 to 11 years. It assesses the control of asthma during the prior 4 weeks. The child completes the first part, which has 4 questions and with a choice of 4 responses to each question. The child should read and respond to each question. If the child needs assistance with reading or understanding the question, the parent/guardian may help; however, only the child should pick a response to the question. The parent/guardian completes the second part, which has 3 questions with a choice of 6 responses ranging from 0 (worse asthma) to 5 (controlled asthma) for each question. The sum of all the responses to the questions provides a score that ranges from 0 (very poor control) to 27 (well-controlled asthma) with a score of more than 19 indicating asthma that is well controlled.

6.4.3 Total Nasal Symptom Score (for Subjects With Known Allergic Rhinitis Only)

The TNSS will be administered only to subjects with known allergic rhinitis at the time points indicated in the Schedule of Events (Appendix 1).

It consists of 5 questions that address nasal congestion, rhinorrhea, nasal itch, sneezing, and difficulty sleeping. Each question has a choice of 4 responses that range from 0 (no symptoms) to 3 (severe symptoms). The subject is asked to recall symptoms over the prior

12 hours to allow calculation of the instantaneous symptom score and then to complete the same questions to address symptoms over the prior 2 weeks for generation of the reflective score.

6.5 Quality of Life Assessments

The questionnaires will be administered to subjects at the time points indicated in the Schedule of Events (Appendix 1). The questionnaires should be completed at the end of the visit after all other visit activities are complete.

6.5.1 Food Allergy Quality of Life Questionnaires and Food Allergy Independent Measure Questionnaires

The Food Allergy Quality of Life (FAQLQ) questionnaires measure health-related QoL in patients with food allergy. The following versions of the FAQLQ forms have been developed.

- Children 8 to 12 years of age (FAQLQ-CF) (Flokstra-de Blok et al, 2009)
- Adolescents 13 to 17 years of age (FAQLQ-TF) (Flokstra-de Blok et al, 2008)
- Adults 18 years of age and older (FAQLQ-AF) (van der Velde, 2009)

Each subject or parent/guardian should complete the same version of the form completed in the ARC007 study, regardless of current age.

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

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

6.6 Immunologic Assessments

Blood samples for immunological assessment will be collected at the time points indicated in the Schedule of Events (Appendix 1) and analyzed at the central laboratory. Additional details for collecting, processing, and shipping these samples may be found in the Central Laboratory Manual. Assessments include peanut-specific and peanut component-specific serum IgE and IgG4 levels.

6.7 Blood Volume

The blood volume collected in children will not exceed the total volume allowed by local ethical guidelines, or 5 mL/kg or a total of 50 mL in 8 weeks. Blood samples will be collected in compliance with local laboratory guidelines and testing regulations.

6.8 Optional Mechanistic Substudies

Subjects in ARC011 are eligible to participate in the optional collection of saliva and peripheral blood specimens for future studies designed to better understand the biological basis and treatment of food allergy. The provision of these additional specimens is voluntary and does not affect the subject's participation in ARC011. The parents/guardian and subject, as appropriate, will be asked to provide informed consent and assent to participate in these substudies.

6.8.1 Blood Storage Substudy

The additional tubes of peripheral blood are to be collected at the same time points as the routine laboratory work in ARC011 and do not require additional visits or phlebotomy. The purpose of this optional substudy is to store blood samples for possible future studies to look at markers in blood that show how the immune system responds to a food allergy

6.8.2 Saliva Substudy Design

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 AEs that interfered with treatment (ie, resulted in reducing, holding, or discontinuing OIT dose levels).

This is an optional substudy which is part of an ongoing collaboration with researchers at Cincinnati Children's Hospital Medical Center to analyze the salivary mRNA transcriptome of participants receiving OIT. Samples will be obtained from ARC011 participants who develop chronic GI symptoms or discontinue the study due to GI symptoms. Only subjects who have provided consent/assent for this substudy are eligible to provide saliva samples.

Saliva samples will be obtained at the time of development of chronic GI symptoms or at the time of withdrawal and at the 6-month time point for those subjects who withdraw from the study.

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/PEESS v2.0 scores) obtained as necessary, and clinical outcome per the ARC007 protocol. Biochemical detection of eosinophil activation products or metabolites may also be possible from collected samples

6.8.3 Saliva Sample Collection and Handling

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 complete blood count (CBC), already collected in ARC011, 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.

6.8.4 Saliva Sample and Data Analyses

The planned analyses include:

- Transcriptome analysis
- EoE diagnostic panel comprising a 96-gene quantitative polymerase chain reaction (qPCR) 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).
- Mass spectrometry
- Flow cytometry
- 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 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. The SVM is a supervised learning model with associated learning algorithms that analyze data and recognize patterns.
- Principle Component Analysis will be employed to categorize the samples globally, 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.

6.9 Safety and Tolerability of AR101 Dosing

6.9.1 Overview

Subjects may develop allergic symptoms following a dose of AR101. Because AR101 contains peanut allergens, dosing symptoms are in general considered to be expected hypersensitivity AEs, which is outlined further in the investigator brochure. Since most doses of AR101 will be given at home, much of symptom reporting in this study will be second-hand. Given the reduced reliability inherent in this situation, 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.

The initial step in evaluating the safety and tolerability of a dose or dose level is to determine how the dose was administered and under what clinical circumstances (eg, intercurrent AE, presence of a co-factor). The investigator must determine the severity of the reported or observed dosing symptoms using his or her judgment, with the CoFAR grading system for hypersensitivity AEs as a guide (Appendix 4). Once determined, the severity of allergic symptoms elicited at a particular AR101 dose will define the tolerability of that AR101 dose. In turn, the determination of tolerability will decide the course of action to be taken in response to dose-related reactions. The location of the dose administration is also important in determining the next course of action, as summarized in text sections to follow and elsewhere in the protocol.

6.9.2 Assessment of the Tolerability of a Dose Level

Table 3 below illustrates the relationship between symptom severity and tolerability of the dose. The greatest need for clinical judgment in determining the tolerability of a dose occurs when the dose elicits one or more mild allergic symptoms. The emergence of moderate and/or severe symptoms indicates that the dose was not tolerated.

Table 3: Allergy Symptom Severity and AR101 Dose Tolerability

Symptom Severity	Assessed Tolerability
None	Tolerated
Mild, oropharyngeal symptoms only	Tolerated
Mild, meeting predefined tolerability criteria (Appendix 4)	Tolerated [1]
Mild, **not** meeting predefined tolerability criteria (Appendix 4)	Not tolerated
Moderate (except for rare exceptions, Appendix 4)	Not tolerated
Severe	Not tolerated

[1] Mild, persistent gastrointestinal symptoms lasting several days may be not tolerated (Section 8.1.4.2).

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

- **No symptoms**: If a dose elicits no symptoms, the dose will be assessed as tolerated.
- **Mild symptoms**: When dosing with AR101 elicits an acute reaction characterized by the appearance of only a mild symptom(s), the investigator will be required to assess whether the dose was or was not tolerated. The determination of tolerability must be made based on clinical judgment. 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 studies, most acute allergic responses to dosing that are characterized by mild symptoms would be anticipated to meet the above criteria. Of note, GI symptoms were the most common potentially allergic symptoms to occur on a subacute, chronic, and/or recurrent basis during the phase 2 AR101 program. If 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 as not tolerated. If a dose administered at home is suspected to have been not tolerated, even based on mild symptoms, the subject should also return to the Clinical Research Center (CRC) for dosing under

medical supervision at the time of the next scheduled dose. 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 source documents.

The recurrence of a mild symptom(s) 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. Further explanation follows; chronic/recurrent GI symptoms are given special consideration:

- If the investigational site is notified of mild dose-related symptoms on 4 or more occasions during a single week, in the absence of an intercurrent AE (See Section 6.9.3 for dose adjustment for intercurrent AEs), 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, in the absence of an intercurrent illness (See Section 6.9.3 for dose adjustment for intercurrent AEs), 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 6.10).
- For any subject having 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 even if mild, owing to the potential for EoE. Further specific instructions for this Adverse Event of Interest can be found in Section 8.1.4.2.

- **Moderate symptoms**: In general, if a dose elicits moderate symptoms, the dose will be assessed as not tolerated. However, there may be rare occasions when a dose eliciting moderate symptoms could be assessed as tolerated. 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, the symptom would be typically subjective only. Any dose associated with moderate symptoms and assessed as tolerated must be accompanied by a brief explanation in the source documents as to why the dose was considered tolerated.
- **Severe symptoms**: 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.

6.9.3 Dose Adjustment in Response to Intercurrent AEs

Emerging evidence from previously published OIT literature and the phase 2 AR101 program suggests that intercurrent illness may affect the tolerability of a dose. Section 5.2 provides guidelines around the preparation and administration of AR101, and outlines the

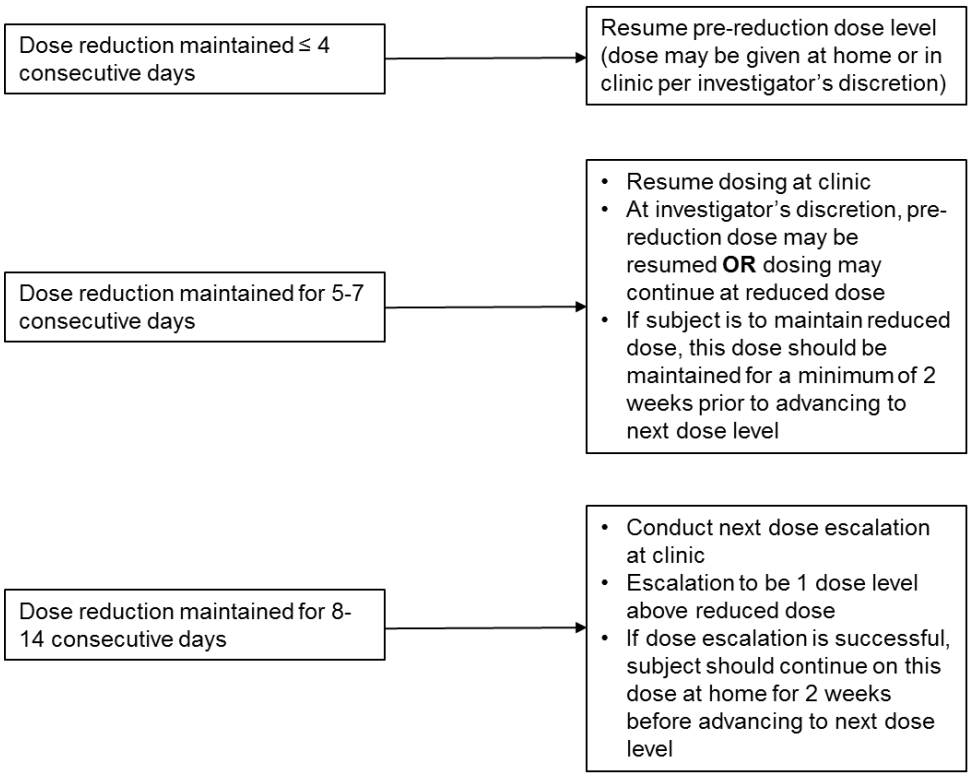
importance of some of these known co-factors. Given that most AR101 doses are administered at home, sites are advised to educate subjects and families about these co-factors (some of which are AEs), as they may first become aware of an intercurrent AE that could create safety concerns. Subjects and/or caregivers should be encouraged to hold the dose and call the study center for guidance if an intercurrent AE develops during the study. Occasionally the AE may only become clinically evident after the dose has already been given. In both cases, dose adjustments may be necessary and are discussed further below.

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.

As an alternative to dose reduction, AR101 may also be temporarily withheld at the investigator's discretion, in response to an intercurrent AE. In some cases (eg, when the intercurrent AE is clinically significant) this may be the most appropriate course of action.

A schematic showing procedures for temporary dose reductions due to intercurrent AEs during the Maintenance Period is provided in Figure 2; explanatory text follows the figure.

Figure 2: Schematic for Temporary Dose Reductions During the Maintenance Period due to Intercurrent Adverse Events



Temporary Dose Reductions During the Maintenance Period

- 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 300 mg maintenance dose may be resumed and the every 4-week visit schedule maintained.
- 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 300 mg maintenance dose may be resumed or dosing may continue at the reduced dose level. If the reduced dose is maintained, the subject's dose will be increased per Section 3.1.3 visit schedule until reaching the 300 mg target dose.
- 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's dose will be increased per Section 3.1.3 until reaching the 300 mg target dose.

Temporary Dose Reductions if Subject is at a Dose < 300 mg

- 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 pre-reduction 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 pre-reduction 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 ≥ 2 consecutive weeks of treatment at the dose level assigned (either the reduced or the pre-reduction 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 withheld as part of the treatment for an AE constitute a special category of missed peanut OIT doses (Section 6.9.3).

6.10 Assessing Symptoms During In-Clinic or Home Dosing

Dosing symptoms in ARC011 may vary by in-clinic administration or administration at home. In-clinic dosing occurs periodically during the Maintenance Period. These doses are administered under direct observation in monitored settings, and only after study procedures that ensure the subject is in general baseline health (eg, a physical exam and PEFR). If a

subject is dosed in the clinic without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the clinic for the next scheduled visit. However, if symptoms arise in the clinic after observed dosing, the investigator will determine whether or not the dose was tolerated (Section 6.9.2). The process algorithm for continued dosing after dose-related symptoms occur in the clinic depends on the study period and is described above for the Maintenance Period and is shown in Figure 2. Dose adjustment after administration of antihistamines and/or epinephrine for dose-related allergy symptoms is described in Section 6.11.

6.11 Treatment for Dosing Reactions: Pharmacologic and Supportive Therapy

The treatment(s) for types of reactions during the study are summarized by severity of reaction in Table 4. The severity of the symptoms in general governs the therapeutic response in accordance with standard-of-care practice.

Table 4: Treatment(s) for Reactions to AR101 During the Maintenance Period by Severity of Reaction

Reaction Severity [1]	Treatment(s)
Mild acute allergic reactions requiring treatment	Antihistamines
Moderate acute symptoms requiring treatment	Antihistamines and/or epinephrine, as indicated
Severe symptoms	Antihistamines and/or epinephrine, as indicated

[1] Assessment of severity of reactions and tolerability of an individual dose is described in Section 6.9.2.

- Treatment of acute reactions should be provided according to the standard of allergy care, 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 transient and 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. This will usually consist of 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.

The procedure(s) that should be implemented after treatment of a reaction to an AR101 dose, including anaphylaxis, during the study are summarized in Table 5. A textual explanation follows the table.

Table 5: Procedure(s) Following Treatment of a Dosing Reaction

Treatment Given for Reaction	Procedure(s) Following Treatment
Epinephrine: 3 or more doses given for dose-related allergy symptoms or anaphylaxis	• Stop study product dosing. • Subject is to return to clinic 14 days after the last dose of study product for the Early Discontinuation Visit (Section 4.4).
Epinephrine given in clinic	• Stop study product dosing. • Reduce next dose by 1 or 2 dose levels per investigator discretion based on the type and severity of the allergy symptoms (Sections 6.9.2, 6.9.3, and 6.10), and administer in clinic under medical supervision. • After continuing the reduced dose after a duration of time recommended by the investigator, dose re-escalation at 1 dose level may be attempted in the clinic. • Following severe allergy symptoms, discussion with the medical monitor is strongly recommended.
Epinephrine given at home	• Instruct subjects to go to the nearest emergency department immediately. • Reduce next dose by 1 or 2 dose levels per investigator discretion based on the type and severity of the allergy symptoms (Sections 6.9.2, 6.9.3, and 6.10), and administer in clinic under medical supervision. • After continuing the reduced dose after a duration of time recommended by the investigator, dose re-escalation at 1 dose level may be attempted in the clinic. • Following severe allergy symptoms, discussion with the medical monitor is strongly recommended.

- Epinephrine – General Procedures

  Any reaction to study product (in clinic or at home) that requires 3 or more 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 4.4).

- Epinephrine – Administered at Clinic

  If administration of epinephrine is required during, or after, a dose in the clinic, or for anaphylaxis, the next dose of study product is to be reduced by 1 or 2 dose levels per investigator discretion based on the type and severity of allergy symptoms (Sections 6.9.2, 6.9.3, and 6.10), and administered in the CRC. After continuing the

reduced dose for a duration of time recommended by the investigator, dose re-escalation at 1 dose level may be attempted in the CRC.

If epinephrine is administered for severe allergy symptoms, discussion with the medical monitor is strongly recommended.

- Epinephrine – Administered 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 a reduced dose (dose reduced by 1 or 2 dose levels per investigator discretion) administered under medical supervision prior to resuming any dosing at home. After continuing the reduced dose for a duration of time recommended by the investigator, dose re-escalation at 1 dose level may be attempted in the CRC.

  If epinephrine is administered for severe allergy symptoms, discussion with the medical monitor is strongly recommended.

7 STUDY VISITS

A study physician must be available at all times during the in-clinic dosing visits.

7.1 Screening/Baseline Visit

Before any unique ARC011-related procedures are performed, the investigator, or designee, must obtain written informed consent/assent for this study from the subject and/or parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline Visit may occur on the same day (or up to 3 days later) as the exit visit of ARC007 and must be completed within 28 days after the signing of the informed consent/assent form. In practice, this means subjects and/or parents/guardian need to be provided with the informed consent/assent forms prior to their completion of the ARC007 study. Initiation of AR101 treatment in this study must be within 3 days after the ARC007 Exit Visit.

The following procedures will be conducted at the Screening/Baseline Visit (ARC011) if not completed at the Exit Visit of ARC007 (or other visit if specified). The Schedule of Events (Appendix 1) identifies the required procedures and delineates which are completed as part of the ARC007 Exit Visit versus those that are conducted solely for ARC011. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 1.

- Inclusion/exclusion criteria review
- Enroll the subject
- Demographics
- Medical history update
- Concomitant medication review
- Food allergen exposure update

- Complete physical examination, including weight and height
- Vital signs
- Completion of questionnaires:
  - ACT/C-ACT Questionnaire (for subjects with known asthma only)
  - TNSS Questionnaire (for subjects with known allergic rhinitis only) –12-hour version and 2-week version
- PEFR (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon])
- Blood sample collection:
  - CBC
  - Immunology assessments
  - Optional volume for immune studies (if consented)
- Urine pregnancy test
- SPT
- Allergic reactions
- Administer AR101
- Postdose vital signs monitoring
- FAQLQ and FAIM Questionnaires

The following procedures will be performed before discharge from the clinic:

- AE recording/SAE recording
- In-clinic dosing
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (see Section 5.2)
- Diary log dispensing

Telephone contact: Site staff will contact the subject or subject's parent/guardian by telephone the next day after this visit to monitor compliance with AR101 dosing, inquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording of, and management of any such events.

7.2 Maintenance Period (Visits Every 4 Weeks for Approximately 6 Months)

In the Maintenance Period, clinic visits will occur every 4 weeks ± 1 week (with the first visit designated as Week 4, Visit 2) until the end of treatment (early discontinuation or study completion, Visit 7).

Some or all of the following procedures will be performed before administration of each in-clinic dose of AR101 and the procedures listed within the Schedule of Events (Appendix 1) should be followed:

- Concomitant medication review
- Food allergen exposure update
- Vital signs
- Abbreviated physical examination
- Allergic reactions
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only)
  - TNSS (for subjects with known allergic rhinitis only) – 12-hour version and 2-week version
- PEFR (should be measured at approximately the same time of day at each visit assessment)
- Diary log review (and dispensing of new diary log, if needed)
- Return of used and unused AR101 sachets/wallets
- Monitoring of compliance
- Administer AR101 in clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.

Some or all of the following procedures will be performed after AR101 dosing and before discharge from the clinic and the Schedule of Events should be reviewed to identify which procedures are performed at each visit:

- Postdose vital signs monitoring
- Monitoring and recording of AEs/SAEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (see Section 5.2)

Site staff will contact the subject or subject's parent/guardian by telephone the next day after Visits 2 through 5 to monitor compliance with AR101 dosing, inquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording of, and management of any such events.

7.3 Exit or Early Discontinuation Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of the study (Exit Visit, Visit 7), subjects will return to the clinic where the investigator must advise the subject or parent/guardian of appropriate options for continued treatment.

Some or all of the following procedures will be performed according to the Schedule of Events (Appendix 1):

- Concomitant medication review
- Food allergen exposure update
- Complete physical examination, including weight and height
- Vital signs
- Completion of questionnaires:
  - PEESS v2.0 (for subjects who discontinue due to chronic/recurrent GI AEs only)
  - ACT/C-ACT (for subjects with known asthma only)
  - TNSS (for subjects with known allergic rhinitis only) – 12-hour version and 2-week version
- PEFR (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC
  - Immunology assessments
  - Optional volume for immune studies (if consented)
- Urine pregnancy test (for female subjects of childbearing potential only)
- SPT
- Optional saliva collection (for early discontinuation subjects only)
- Allergic reactions
- Diary log review
- Return of any unused AR101
- Monitor compliance
- In-clinic dosing of AR101 (Exit Visit only)
- Postdose vital signs monitoring
- Monitoring and recording of AEs/SAEs, including allergic symptoms
- FAQLQ and FAIM Questionnaires
- Peanut allergy training

Subjects who have chronic/recurrent GI AEs at the Exit Visit will complete the PEESS v2.0 questionnaire and return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management or the investigator deems them to be irreversible.

7.4 Unscheduled Visit

A subject may return to the clinic between scheduled visits to have the AR101 dose adjusted, because of AEs or lack of tolerance to the current dose regimen or for other reasons as required by the investigator.

The procedures performed at unscheduled visits may include any or all of those listed in Appendix 1.

7.5 Unscheduled Blood Sample

If a subject or subject's parent/guardian declares his or her intention to discontinue AR101 dosing, whether at a scheduled visit or an unscheduled visit, a blood sample should be collected for CBC and immunologic assessments assays.

If a blood sample is collected at this time, the corresponding blood sample is not required at the Exit Visit.

8 ADVERSE EVENTS AND SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in humans, whether or not considered related to the IP, that occurs during the conduct of a clinical study. Any change in clinical status, electrocardiograms, routine laboratory results, x-rays, physical examinations, etc, that is considered clinically significant by the study investigator is considered an AE.

In addition, any pregnancy diagnosed in a female subject during treatment with an IP will be collected as an AE. The pregnancy will be reported to the Safety Reporting Center within 24 hours of knowledge of the pregnancy.

8.1.2 Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IP caused the AE. A reasonable possibility implies that there is evidence that the IP caused the event.

An adverse reaction is any AE caused by the IP.

8.1.3 Serious Adverse Event

An SAE 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 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.

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.

8.1.4 Adverse Events of Interest

8.1.4.1 Anaphylaxis

Anaphylactic AEs will be considered AEI. Anaphylaxis is defined by a number of signs and symptoms, alone or in combination, which occur within minutes, or up to a few hours, after exposure to a provoking agent. It can be mild, moderate, or severe. Most cases are mild but any event of anaphylaxis has the potential to become life-threatening. The clinical criteria for defining anaphylaxis have been adopted for this study from the second symposium on the definition and management of anaphylaxis of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (Sampson et al, 2006), and are consistent with the recently published international consensus on anaphylaxis (Simons et al, 2011).

The clinical criteria for suspected anaphylaxis are defined in Appendix 2 and the severity grading parameters are listed in Appendix 3. When the diagnosis of anaphylaxis is made, the basis for having suspected the diagnosis must be documented using these criteria.

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 Definitions and Standards for Expedited Reporting in the ICH-E2A Tripartite Guideline, which states the following:

> 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 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 European Academy of Allergy and Clinical Immunology (EAACI) system for grading the severity of anaphylactic reactions (Muraro et al, 2007), is also to be taken into account (Section 8.2.4 and Appendix 3).

8.1.4.2 Gastrointestinal AEs Resulting in Prolonged Disruption of Dosing

GI AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will also be considered AEIs and will be assessed longitudinally according to the procedures described below. EoE presents with varied symptoms of esophageal dysfunction that differ between children and adults (Dellon, 2011; Dellon et al, 2013). In children, the symptoms are often nonspecific and may include feeding difficulties, failure to thrive, abdominal pain, regurgitation, nausea, and vomiting. In adults, the most frequent symptoms are dysphagia and food impaction; less frequent symptoms include heartburn, chest pain, abdominal pain, nausea, or vomiting. Special attention should be paid to these symptoms, which may suggest esophageal dysfunction, particularly when the symptoms are new in onset during the study, chronic or recurrent, or experienced as a complex of multiple symptoms.

To delineate these AEIs, prolonged disruption of dosing is defined as withholding AR101 for > 7 days. This will include 2 categories of subjects:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level
- Any subject who permanently discontinues dosing who had experienced GI AEs

Subjects who fall into any of these 2 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent/guardian, as appropriate, at the point of treatment discontinuation and then every month for 6 months thereafter. The PEESS v2.0 questionnaire is being used in an exploratory manner to assist the clinician in the monitoring of GI symptoms.

Subjects who discontinue dosing prematurely due to chronic/recurrent GI AEs will be requested to return to the clinic for evaluation monthly for at least 6 months (if the subject is asymptomatic, telephone follow-up with a physician investigator may substitute for in-clinic visit, at the investigator's discretion). If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits 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 IP, the subject should be referred to a (pediatric) gastroenterologist.

If a subject who discontinued dosing with the IP 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 IP was withdrawn, the subject should be referred to a (pediatric) gastroenterologist.

As is the case for any AE occurring during the study, for chronic/recurrent GI AEs the investigator may use discretion anytime to 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 will attempt to procure records of the visit, as well as any test results, including those from endoscopy and endoscopic biopsy, if performed. These results will be retained with the subject's medical notes.

8.1.4.3 Accidental and Nonaccidental Food Allergen Exposures

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

Subjects will record accidental or nonaccidental food allergen exposures in the daily dosing diary.

Subjects will be instructed to contact the site study coordinator or investigator after any known or suspected food allergen exposure, even if it does not cause symptoms. The subject may be asked to return to the site for further evaluation. These events will be reported as follows:

- The nonserious AEI form will be completed for each of these events, in addition to events where consumption of peanut without a reaction occurs, *unless*:
- The accidental/nonaccidental food ingestion safety event meets the definition of an SAE, as defined in Section 8.1.3, in which case the SAE form will be completed.

If an accidental/nonaccidental food allergen exposure does not result in an AE, no assessment of severity, seriousness, or relatedness is required.

8.1.4.4 Adverse Events Featuring a Severe Symptom

Any AE meeting the criteria for severe as defined in Section 8.2.4 will be reported as an AEI. The severity of symptoms will be determined on the basis of the investigator's judgment. Severity definitions for allergic reactions to IP were developed to be consistent with the CoFAR grading system and are provided in Appendix 4.

8.1.4.5 Adverse Events Associated With Use of Epinephrine

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

8.1.5 Unexpected Adverse Event

An AE is unexpected when its nature, severity, or specificity is not consistent with applicable product information such as safety information provided in the package insert, the investigational plan, the investigator brochure, or the protocol.

8.1.6 Clinically Significant Laboratory Results

An abnormal test result usually warrants reporting as an AE in the following situations:

- The test result is associated with clinical symptoms or signs and/or;
- The test result requires additional diagnostic testing or medical/surgical intervention and/or;
- The test result leads to a change in dosing or discontinuation of study treatment.

8.2 Adverse Event Monitoring and Recording

8.2.1 Monitoring Procedures

All AEs will be recorded from the time of signing of the ICF through the Exit or Early Discontinuation Visit or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is later.

The investigator will treat subjects experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

Any new event or experience that was not present at Screening/Baseline or worsening of an event present at Screening/Baseline will be reported as an AE. Unchanged, chronic conditions are not AEs and should not be recorded on the AE form of the eCRF.

Each subject will be provided a diary log to record any AEs between study visits. Additionally, AEs may be discovered through any of the following 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/medical notes

SPT reactions are not considered an AE unless the reaction, or a complication from the procedure, is considered an SAE, as defined in Section 8.1.3.

8.2.2 Recording Procedures

All AEs will be recorded in the source documents from the time of signing of the ICF through the Exit Visit or Early Discontinuation Visit. Recording of these AEs into the eCRF

is described in the eCRF completion guidelines. In addition, SAE and AEI will be entered in a respective AE Pharmacovigilance Form as detailed in the AE Form completion guidelines. Completion of the appropriate AE Form is summarized in Table 6 below.

Any event that meets the definition of an SAE (Section 8.1.3) will also be reported to the Study Safety Reporting Center using an SAE report form as described in Section 8.3 in addition to completing the AE form. SAE follow-up reports should include, as applicable, 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. In the event of a death, other supporting data (eg, death certificate, medical notes) should be included. Source documents, with subject identifiers redacted, can be scanned and attached to the AE form as well.

Table 6 Reporting Forms for Serious Adverse Events, Adverse Events, Pregnancies, and Other Events

Adverse Event Type (Reference Section)	PV Form	Severity Criteria	Timeline	Follow-Up
Serious Adverse Event Section 8.1.3	SAE Form		≤ 24 hours	Yes
AEI: Anaphylaxis Section 8.1.4.1	AEI Form (unless SAE)	Muraro et al, 2007/EAACI Appendix 3	≤ 24 hours	Yes
AEI: Gastrointestinal AE resulting in dosing disruption Section 8.1.4.2	AEI Form	NCI-CTAE Section 8.2.4	≤ 24 hours	Yes
AEI: Accidental Food Allergen Exposure Section 8.1.4.3	AEI Form		≤ 24 hours	Yes
AEI: AE associated with epinephrine use Section 8.1.4.5	AEI Form		≤ 24 hours	Yes
AEI: Severe AE Section 8.1.4.4	AEI Form		≤ 24 hours	Yes
Other: Pregnancy Section 8.1.1	Pregnancy Form	NCI-CTAE Section 8.2.4	≤ 24 hours	Yes
Other: Nonserious Section 8.1.4.1-8.1.4.5	AEI Only		< 7 days	Yes
All AEs Section 8.2.1-8.2.2	Not Applicable (use eCRF)		Within 7 days of site awareness	

AE = adverse event; AEI = adverse event of interest; eCRF = electronic case report form; NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PV, pharmacovigilance; SAE = serious adverse event.

8.2.3 Safety Monitoring Committee

Although the safety of peanut OIT overall is well established, an internal SMC will monitor the safety of the study in accordance with internal procedures. The SMC consists of individuals with extensive multicenter clinical study experience drawn from the fields of clinical immunology (specifically food allergies) and biostatistics. The SMC meets at least quarterly throughout the study to review accruing safety data.

8.2.4 Assessment of Severity

The investigator will assign severity grades to AEs. Depending on the type of AE, the following severity grading systems will be used in this study:

- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 3).
- The severity of allergic reactions will be graded according to the definitions developed by the CoFAR group (Appendix 4).
- The severity of all other AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) system. 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 AE. 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.
- AEs not included in the NCI-CTCAE listing will also to be graded on a scale from 1 to 5, according to the General Grade Definition:
  - **Grade 1 (Mild):** Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (nonprescription or single-use prescription therapy may be employed to relieve symptoms (eg, aspirin for simple headache, acetaminophen for postsurgical 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)**

8.2.4.1 Assessment of Causality (Relatedness)

The investigator will use the following criteria when assessing causality of an AE to IP:

Related	There is a reasonable possibility that the study drug caused the event.
Not Related	There is NOT a reasonable possibility that the study drug caused the event. Adverse events assessed as not related will require an assessment of alternative causality.

8.3 Serious Adverse Event Reporting Procedures

All SAEs will be reported to the sponsor from the time of signing of the ICF through the Exit Visit or Early Discontinuation Visit. If the investigator becomes aware of a SAE in a subject treated by him or her with a suspected causal relationship to the IP that occurs after the end of the study, the investigator shall, without undue delay, report it to the sponsor.

SAEs will be recorded on the AE eCRF. The site will also report an SAE to the Safety Reporting Center within 24 hours of the site's knowledge of the event using an SAE report form. The following attributes will be included in an SAE report:

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

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

Subsequent review by regulatory authorities, the SMC, IRBs/ECs, or the sponsor may suspend further trial treatment or procedures at a site. The study sponsor and the regulatory authorities retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

8.4 Serious Adverse Event Notification

8.4.1 Notifying the Sponsor

The Safety Reporting Center will notify the sponsor within 24 hours of receiving the report from the site.

8.4.2 Expedited SAE Reporting to Health Authorities

A medical monitor will review each SAE report and will determine whether the SAE must be reported to regulatory authorities on an expedited basis. The final decision for disposition regarding expedited reporting to the regulatory authorities rests with a medical monitor. The sponsor will provide the Safety Reporting Center with copies of any expedited SAE reports submitted to regulatory authorities.

The sponsor will expedite the reporting to all concerned investigator(s), IRBs/ECs, where required, and to the national regulatory authorities of all suspected unexpected serious adverse reactions (SUSARs) in accordance with ICH E6 5.16.2 and 5.17.1. In addition, such expedited reports will comply with the applicable regulatory requirement(s) and with the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and ICH E6 5.17.2.

The Safety Reporting Center will provide these expedited reports to each investigator. SAEs that are deemed related to IP and are unexpected will be reported to regulatory authorities within 15 days or for deaths and life-threatening events within 7 days (in accordance with applicable regulatory reporting requirements).

The sponsor will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements including ICH E6 5.17.3 and ICH E2F.

8.4.3 Notifying the Safety Monitoring Committee

The Safety Reporting Center will provide the SMC (Section 8.2.3) with listings of all SAEs on an ongoing basis. Furthermore, the SMC will be informed of expedited SAE reports. The SMC will send periodic reports on the overall safety of the ongoing study and recommendations regarding continuation, and investigators will forward to the IRBs/ECs if required.

Sites will report episodes of anaphylaxis within 24 hours of the sites being notified of the event to the Safety Reporting Center for forwarding to the SMC if the event is associated with any of the following:

- An ER visit
- Hospitalization
- Three or more 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 the time will be transmitted to the Safety Reporting Center. The Safety Reporting Center will then relay to the sponsor and SMC the individual anaphylaxis reports as they are obtained. The 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 Safety Reporting Center.

8.4.4 Notifying the Institutional Review Boards and Ethics Committees

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

8.5 Study Discontinuation

The sponsor reserves the right to terminate the study any time for any reason, including upon commercial product availability. Regulatory authorities and IRBs/ECs will be notified in the event of study termination.

9 STATISTICAL CONSIDERATIONS

Full details of the statistical methods to be used in the analysis and data handling for this study will be described in a statistical analysis plan (SAP). Any deviation from the SAP will be described in the Clinical Study Report.

9.1 Sample Size

There is no sample size calculation for this study. This study is an extension of ARC007 (RAMSES) for subjects who received AR101 OIT. Therefore, the number of subjects who are potentially eligible to enroll is approximately 330. This is based on a target enrollment of 500 subjects in ARC007 and a 2:1 AR101: Placebo randomization.

9.2 Analysis Conventions

Data will be summarized using descriptive statistics. No specific hypothesis testing or comparisons are planned for this study.

Continuous data (ie, age, body weight, and height) will be summarized descriptively using mean, standard deviation, median, and range. Categorical data (ie, sex and race) will be presented as enumerations and percentages.

Data will be listed for each subject.

9.3 Analysis Populations

The primary population for all analyses will be the safety population, which will consist of all subjects who receive IP during ARC011.

9.4 Interim Analysis

Interim data analyses may be performed as needed to summarize safety data.

9.5 Subject and Demographic Data

9.5.1 Study Disposition

The number of subjects who complete the study or who discontinue the study prematurely and reasons for study discontinuation will be tabulated. Total duration of AR101 treatment will also be summarized.

9.5.2 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic data will be provided for all subjects in the safety population.

9.5.3 Use of Medications

All medications used will be coded using the World Health Organization international drug classification dictionary (WHODrug). The number and percentage of subjects receiving concomitant medications or therapies will be summarized descriptively.

9.6 Efficacy Analyses

The objective of this study is to obtain safety information in subjects who received AR101 treatment. There will be no analysis of efficacy endpoints in this study.

9.7 Safety Analyses

All safety endpoints will be summarized using descriptive statistics. Further details will be provided in the SAP.

AEs will be coded based on the Medical Dictionary for Regulatory Activities terminology. Events will be tabulated by system organ classification and preferred term.

10 STUDY DATA

10.1 Electronic Data Capture System

Data will be collated using an electronic data capture (EDC) system to allow easy access to enrollment 24 hours a day, 7 days a week. As data are entered, they will be validated using range and within-form consistency checks. The investigator must ensure that all eCRFs are completed in a timely fashion for all subjects at his or her site.

Access to the EDC system will be password controlled.

The clinic and laboratory staff will be trained in the use of the EDC system by telephone or web-cast training. Once certified, users will be permitted to enter data into the EDC system.

10.2 Access to Data

The investigational sites will periodically permit authorized representatives of the study sponsor or regulatory authorities to examine clinical records and other medical notes for safety monitoring, quality assurance review, audit, or 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-GCP) to keep accurate case records for at least 2 years after acceptance of a licensure application and record observations to assure the safe conduct of the study, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and Regulatory Authorities are notified, or longer if required by local regulations.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Statement of Compliance

This study will be conducted using current GCP, as delineated in the 21 CFR Parts 50, 54, and 312 and in the ICH-GCP, national and international regulations and directives as appropriate, and according to the study protocol. Before study initiation, the protocol and the informed consent and assent documents will be reviewed and approved by an appropriate IRB/EC and the applicable regulatory authority of each country in which the study is conducted. Any amendment to the protocol must also be approved by the sponsor, SMC, and IRB/EC and submitted to the applicable regulatory authorities before it is implemented. Any amendment to the consent/assent materials must also be approved by the sponsor and the IRB/EC before it is implemented.

11.2 Informed Consent and Assent

The ICF will be provided to each prospective adult subject or prospective pediatric subject's parent/guardian to allow for an informed decision about participation in the study. An age-appropriate assent form will also be provided to each prospective pediatric subject for review.

The subject and/or parent/guardian will be allowed as much time as needed to review the document(s) and consider participation in the study. The investigator, or designee, will review the consent/assent, answer any questions, and emphasize the need to avoid allergen exposure other than IP and the necessity to continue IP dosing to maintain desensitization. The prospective subject and/or pediatric subject's parent/guardian will be told that being in the study is voluntary and that the subject may withdraw from the study any time and for any reason. Adult subjects and parents/guardians of pediatric subjects will each sign the ICF, and pediatric subjects will each sign the assent form, as required by the IRB/EC. Where required, both parents will sign the consent form before a child can be enrolled in the study. The subject or subject's parent/guardian must be given a copy of the signed and dated ICF and assent form, if used. Written informed consent and assent must be obtained before any study-related procedure is performed.

Informed consent/assent materials will be translated into appropriate languages for subjects and parents/guardians who do not speak or read English. The informed consent/assent form will be evaluated for revision whenever the protocol is amended or new safety information becomes available.

11.3 Privacy and Confidentiality

Each 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.

11.4 Study Monitoring

Before the start of the study, the sponsor's monitor will meet with the investigator and appropriate investigational site staff for training on the protocol requirements and procedures.

Throughout the course of the study, the sponsor's monitor will conduct site visits to verify that the rights and well-being of the subjects are protected; the reported study data are accurate, complete, and verifiable from medical notes; and that the conduct of the study is in compliance with the currently approved protocol, GCP, and applicable regulatory and legal requirements.

11.5 Data Management

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.

12 RESOURCE SHARING

All data derived from this study will be sent to the Reporting Center for storage and analysis. Subject data will be anonymous to maintain subject confidentiality. All important findings 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 investigational site staff will conduct the study in accordance with the protocol. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Whenever applicable, protocol deviations will result in development of corrective and preventive actions by the site and prompt implementation.

Where necessary, the Investigator can implement a deviation to the protocol to eliminate an immediate hazard to a study subject, although every effort should be made to discuss this with the sponsor's medical monitor beforehand.

Protocol deviations must be clearly documented including the reasons for the deviations. The principal investigator is responsible for reporting protocol deviations in accordance with their local IRBs/ECs requirements. Where protocol deviations lead to the protocol being amended, the amended protocol will be submitted to the relevant IRB/EC and regulatory authorities for review, as appropriate.

13.1 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document, and report protocol deviations and appropriate corrective and preventive action plans; however, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

All protocol deviations will be reported in accordance with the protocol deviation plan.

14 BIOLOGICAL SAMPLES

Biological samples collected for this study will become the property of the sponsor. No identifiable personal information will be associated with these blood samples. After completion of the sample analysis, no samples will be stored, and any remaining blood will be destroyed.

15 FINANCING AND INSURANCE

Financing and insurance will be addressed in a separate clinical study agreement.

16 REFERENCE LIST

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17 APPENDICES

Appendix 1: Schedule of Events

Procedure	Screening/ Baseline Visit	Maintenance Period (~24 Weeks)						Early Discontinuation Visit	Unscheduled Visit[r]
	Same Day as Exit Visit for ARC007 (+3 Days)	Visits Every 4 Weeks (± 1 Week)						14 days (-3/ +7 Days) Post Last Dose of AR101	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (Exit)**		
Week of Study	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Informed consent and/or assent[a]	X								
Inclusion/exclusion criteria	X								
Enrollment[c]	X								
Demography	X								
Updated medical history[b]	X								
Concomitant medications	X[s,t]	X	X	X	X	X	X	X	X
Food allergen exposure update	X[s,t]	X	X	X	X	X	X	X	X
Vital signs[d]	X[s]	X	X	X	X	X	X	X	X
Complete PE[e]	X[s,t]						X	X	
Abbreviated PE[z]		X	X	X	X	X			X
Adverse events/serious adverse events[f]	X	X	X	X	X	X	X	X	X
Allergic reactions[g]	X	X	X	X	X	X	X	X	X
C-ACT (< 12years) or ACT[h]	X[s,h]	X	X	X	X	X	X	X	X
TNSS questionnaire[i]									
• 12 hour	X[s,v]	X					X	X	X
• 2 week	X[s,v]	X					X	X	X
FAQLQ (completed by subject and parent/guardian)/FAIM[j]	X[s,t]						X	X	
PEFR[k]	X[s,t]	X	X	X	X	X	X	X	X
Review diary/dispense new diary	X[s]/X	X/X	X/X	X/X	X/X	X/X	X/NA	X/NA	X/X
Home dosing instructions	X	X	X	X	X	X			
Monitor compliance	X[s,t]	X	X	X	X	X	X	X	X
Skin prick test	X[s,v]						X	X	
Blood draw for:									
• Complete blood count[x]	X[u]						X	X	X
• Peanut-specific IgE, IgG4[x]	X[u]						X	X	X
• Optional volume for immune studies[l,x]	X[u]						X	X	X
Urine pregnancy test[w]	X[s,t]						X	X	X

Procedure	Screening/ Baseline Visit	Maintenance Period (~24 Weeks)						Early Discontinuation Visit	Unscheduled Visit[r]
	Same Day as Exit Visit for ARC007 (+3 Days)	Visits Every 4 Weeks (± 1 Week)						14 days (-3/ +7 Days) Post Last Dose of AR101	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (Exit)**		
Week of Study	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Optional saliva collection[m]								X	X
In-clinic dosing	X	X	X	X	X	X	X		X
Dispense/return AR101[n]	X	X	X	X	X	X	X	X	X
Postdose vital signs[o]	X	X	X	X	X	X	X		X
Peanut allergy training	X	X	X	X	X	X	X[y]	X	X
PEESS v2.0[p]								X	X
Telephone follow-up[q]	X	X	X	X	X	X			X

ACT = Asthma Control Test; AE = adverse event; C-ACT = Childhood Asthma Control Test; FAIM = Food Allergy Independent Measure; FAQLQ = Food Allergy Quality of Life Questionnaire; GI = gastrointestinal; IgE = immunoglobulin E; IgG4 = immunoglobulin G subclass 4; PE = physical examination; PEESS v2.0 = Pediatric Eosinophilic Esophagitis Symptom Scores questionnaire, version 2.0; PEFR = peak expiratory flow rate; TNSS = Total Nasal Symptom Score.

a) May be obtained up to 28 days prior to Screening/Baseline Visit Day
b) Any new condition that developed and resolved during the ARC007 study should be included as medical history
c) Enroll subject using a web-based interactive response system
d) Includes blood pressure, pulse and temperature taken predose on dosing days
e) Includes height and weight
f) 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. GI symptoms are to be followed until either resolution or 6 months has passed
g) From diary and questioning the subject
h) Only for subjects with known asthma. Repeat if > 4 weeks since last completed
i) For subjects with known allergic rhinitis
j) Questionnaire age group should not change from ARC007 baseline
k) For subjects ≥ 6 years of age, obtain PEFR at approximately the same time of day for each assessment visit (eg, morning, afternoon); record the best result of 3 attempts. If PEFR shows a clinically relevant reduction or clinical deterioration (eg, active wheeze on physical examination) or as clinically indicated on unscheduled visits, obtain spirometry (FEV_1); record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment).
l) For subjects who have consented for this optional procedure
m) For subjects who have consented
n) See pharmacy manual for details
o) Blood pressure, pulse within 15-30 minutes after dose
p) For subjects with GI AE whose dose is held > 7 days and resume dosing at a lower dosage or early withdrawal due to GI AEs
q) Occurs one day after visit

Procedure	Screening/ Baseline Visit	Maintenance Period (~24 Weeks)						Early Discontinuation Visit	Unscheduled Visit[r]
	Same Day as Exit Visit for ARC007 (+3 Days)	Visits Every 4 Weeks (± 1 Week)						14 days (-3/ +7 Days) Post Last Dose of AR101	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (Exit)**		
Week of Study	**0**	**4**	**8**	**12**	**16**	**20**	**24**		

r) Any of the procedures below may be performed
s) As part of Exit Visit for Study ARC007
t) Repeat if > 3 days since last completed
u) As part of the 300 mg Visit for ARC007 or the last unscheduled visit when a blood sample was collected. Repeat if > 6 weeks since last collected
v) Repeat if > 6 weeks since last completed
w) For sexually active females of childbearing potential only
x) After the predose vital signs and PEFR and before administration of AR101
y) Only for subjects not entering ARC008. If subjects enter ARC008, peanut allergy training will be done as part of the screening procedures for ARC008.
z) Symptom-directed

Appendix 2: Criteria for Suspected Diagnosis of Anaphylaxis

Criteria for Suspected Diagnosis (adapted from Sampson et al, 2006)

Anaphylaxis is likely when any 1 of the 3 following sets of criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) 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 PEFR) 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 (minutes to hours):
   - Skin/mucosal tissue (eg, *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   - Airway compromise (eg, dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEFR)
   - 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 (minutes to hours):
   - 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.

Appendix 3: Criteria for Anaphylaxis Severity Grading

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

Staging System of Severity of Anaphylaxis	
Stage	**Defined by**
1. *Mild* (skin and subcutaneous tissues, GI, and/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 and 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

For an episode of anaphylaxis to be considered an SAE, the sponsor advises that the event satisfies one of the outcome-based definitions of SAE specified in Section 8.1.3 of the protocol, with the stipulations (denoted in *italics*) indicated. These stipulations follow from, and are consistent with, the criteria for reporting to the internal SMC (Section 8.3):

1. Death – *No further stipulation*.
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.): *For anaphylaxis to be considered life-threatening, it should be assessed to have been severe, and of a Grade 4 allergic reaction, as defined* in Appendix 4. 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.
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: *No further stipulation*.
4. Congenital abnormality or birth defect: *No further stipulation*.
5. 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 an SAE:
   - 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 ER visit, and the ER 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 4: Allergic Reaction Severity Grading

The CoFAR grading system (Burks et al, 2012) for allergic reactions is displayed in the table.

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 or hospice care 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

Specific symptoms that are generally consistent with this severity grading scheme are provided below as illustrative examples:

- Mild symptoms:
  - Skin – limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema), or pruritus (eg, causing mild occasional scratching)
  - Respiratory – rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort
  - 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 2).