CLINICAL STUDY PROTOCOL

ARC010
AR101 Trial in Europe Measuring Oral Immunotherapy Success in Peanut Allergic Children (ARTEMIS)

Protocol Version 4.0, Amendment 3.0 – 28 Aug 2018
Reference Numbers: NCT03201003, EudraCT 2016-005004-26

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CLINICAL STUDY PROTOCOL

Protocol Title:	**AR**101 **T**rial in **E**urope **M**easuring Oral **I**mmunotherapy **S**uccess in Peanut Allergic Children (ARTEMIS)
Study Phase:	Phase 3
Investigational Drug	AR101
Protocol Number:	ARC010
IND Number:	15463
EudraCT Number:	2016-005004-26
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Blvd, Suite 300 Brisbane, CA 94005 United States

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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 ARC010
Sponsor Personnel

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Principal Investigator Protocol Approval

Protocol ARC010	Protocol 4.0 (Amend 3.0) Date: 28 Aug 2018
IND: 15463 EudraCT: 2016-005004-26	
Short Title: ARTEMIS	

I have read this clinical study protocol. 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

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
Short Title	ARTEMIS
Clinical Phase	3
IND	15463
EudraCT	2016-005004-26
IND Sponsor	Aimmune Therapeutics, Inc.
Number of Subjects	Approximately 160 peanut-allergic subjects will be randomized 3:1 to AR101 peanut oral immunotherapy (OIT) versus placebo.
Objectives	The primary objective is to demonstrate the efficacy of AR101, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children and adolescents (ages 4 to 17 years, inclusive). The secondary objectives are: • To demonstrate the safety of AR101 as measured by the incidence of adverse events (AEs), including serious adverse events (SAEs). • To evaluate the immunological effects of peanut OIT therapy.
Study Design	This is a European, multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in a characterized desensitization OIT regimen in peanut-allergic individuals. The study will consist of a Screening phase that includes a Screening double-blind, placebo-controlled food challenge (DBPCFC), and a double-blind OIT treatment phase that includes an Initial Escalation Period, an Up-dosing Period, and a Maintenance Period, followed by an Exit DBPCFC. Eligible subjects will receive escalating doses of either AR101 or placebo. Eligible subjects who reach the targeted dose of 300 mg/d and maintain that dose for approximately 12 weeks will undergo an Exit DBPCFC; subjects may have a dose reduction because of an AE but must be on a dose of 300 mg/d without symptomatic therapy for the 4 weeks immediately preceding the Exit DBPCFC. Subjects who do not reach the maintenance dose of 300 mg/d will be discontinued from the study. An Exit DBPCFC will be performed for those subjects achieving the target dose of 300 mg/d and continuing to receive that dose throughout the Maintenance Period (approximately 12 weeks). Each subject will be unblinded when he/she completes the Exit DBPCFC at the end of the approximately 12-week Maintenance Period, all major data queries (ie, queries that could influence allocation to 1 or another analysis population) for the subject have been resolved, and the follow-on study ARC008 is available at the study site. All placebo-treated subjects who complete ARC010 are eligible for rollover into the follow-on study ARC008. In the follow-on study, placebo-treated subjects from ARC010 will undergo an initial escalation and up-dosing schedule identical to that for subjects who received AR101 in ARC010. All AR101-treated subjects in ARC010 who tolerate the single challenge dose of 300 mg peanut protein (443 mg cumulative) during the Exit DBPCFC are eligible to proceed to the follow-on study. Subjects who complete 12 weeks of maintenance and experience dose-limiting symptoms (DLS) at the exit challenge at the dose of 300 mg peanut protein (443 mg cumulative) or below will not be eligible to enroll in ARC008. If ARC008 is not yet available at the study site, subjects may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	available. Subjects who do not tolerate 300 mg peanut protein at the Exit DBPCFC will not continue blinded study treatment in ARC010. The end of the study is defined as the last visit of the last subject. A Data Safety Monitoring Committee (DSMC) will be established to monitor the study for safety.
Study Duration	Each subject will participate in the study for up to approximately 14 months. The expected duration of the study is approximately 18 months.
Primary Endpoint	The primary clinical efficacy endpoint is the proportion of subjects who tolerate at least 1000 mg as a single dose (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC.
Secondary Efficacy Endpoints	<u>Key Secondary Efficacy Endpoints</u> • The proportion of subjects who tolerate at least 600 mg as a single dose (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The proportion of subjects who tolerate at least 300 mg as a single dose (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The maximum severity of symptoms occurring following ingestion of peanut protein during the Exit DBPCFC <u>Other Secondary Efficacy Endpoints</u> • Maximum tolerated dose (MTD) with no more than mild symptoms at Exit DBPCFC • Change from baseline in MTD of peanut protein at Exit DBPCFC • Use of epinephrine as a rescue medication at Exit DBPCFC and comparison to its use at Screening DBPCFC • Changes in serum peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 levels • Changes in peanut skin prick test (SPT) mean wheal diameter • Quality of life assessment using the food allergy quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire <u>Exploratory Endpoints</u> • Treatment satisfaction assessment using the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and an Exit Questionnaire. • Assessment of palatability (taste and after-taste)
Safety Endpoints	• The safety of peanut OIT based on AEs and SAEs • Use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) • Frequency and severity of anaphylaxis during OIT (Initial Escalation, Up-dosing, and Maintenance Periods), attributable to investigational product (IP) or accidental food exposure • Frequency and severity of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the Maintenance Period, normalized for duration of treatment

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	• Frequency of accidental ingestion of peanut and other allergenic foods; frequency and severity of reactions resulting from accidental ingestion of peanut and other allergenic foods • Frequency and severity of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs • Assessment of asthma control using the 2007 National Heart, Lung, and Blood Institute (NHLBI) classification and the Asthma Control Test questionnaire in subjects with asthma
Investigational Product and Dispensing	AR101 or placebo. Doses characterized and normalized for total protein and specific peanut allergen ratios will ascend per the dosing regimen in the Initial Escalation Period Dosing Schedule and Up-dosing Period Dosing Schedule at the end of the synopsis. IP will be provided in pull-apart capsules formulated to contain 0.5, 1, 10, 20, and 100 mg of peanut protein. Matching placebo capsules identical to the active capsules will be used to maintain the blind. Capsules for dose escalation and up-dosing will be supplied in blister packs. For the Maintenance Period, 300 mg of peanut protein will be supplied in foil-laminate sachets. Matching placebo sachets will be used to maintain the blind. Trained investigational site personnel will dispense the IP to the subject's parent or guardian in a manner consistent with the assigned dose level. IP will be dispensed in a double-blinded fashion according to subject randomization number, using a proprietary interactive response system.
Inclusion Criteria	• Age 4 through 17 years (inclusive) • Clinical history of allergy to peanuts or peanut-containing foods • Serum IgE to peanut ≥ 0.35 kU_A/L, inclusive (as determined by UniCAP™ within the past 12 months) and/or a peanut SPT wheal diameter ≥ 3 mm compared to control • Experience DLS at or before the 300 mg (444 mg cumulative) challenge dose of peanut protein (measured as 600 mg of peanut flour) on Screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines • Written informed consent from subject or parent/guardian for all subjects (or both parents when required by local authorities) • Written assent from minor subjects as appropriate (in accordance with local regulatory requirements) • Use of effective birth control by female subjects of childbearing potential (Section 7.10.3.2)
Exclusion Criteria	• History of hemodynamically significant cardiovascular disease, including uncontrolled or inadequately controlled hypertension (Section 5.10) • History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of Screening DBPCFC • History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of, becoming unstable or requiring a change in chronic therapeutic regimen including autoimmune diseases and malignancies (including malignancies occurring in the 5 years prior to Screening)

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	• History of eosinophilic esophagitis (EoE), other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"), or recurrent GI symptoms of undiagnosed etiology • Current participation in any other interventional study and/or participation in another interventional clinical study within 30 days or 5 half-lives of the IP, whichever is longer, prior to randomization • Participation in, and having received active treatment in, any previous clinical study of AR101 CODIT™ • Currently receiving, or having received in the 5 years prior to Screening, any type of peanut or any other food immunotherapy (including subcutaneous, sublingual, oral, or epicutaneous) • Subject is in "build-up phase" of immunotherapy to another allergen (ie, has not reached maintenance dosing) • Severe asthma (2007 NHLBI Criteria Steps 5 or 6, Appendix 2) • Mild or moderate asthma (2007 NHLBI Criteria Steps 1-4), if uncontrolled or difficult to control as defined by any of the following: o Forced expiratory volume in 1 second (FEV_1) < 80% of predicted, with or without controller medications (only for age 6 years or greater and able to do spirometry); *or* o Inhaled corticosteroid (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICS based on NHLBI dosing chart); *or* o 1 hospitalization in the past year prior to Screening for asthma; *or* o Emergency room (ER) visit for asthma within 6 months prior to Screening • History of high-dose corticosteroid use (eg, 1 to 2 mg/kg of prednisone or the equivalent for > 3 days) by any route of administration in any of the following manners: o history of daily corticosteroid dosing for > 1 month during the past year; *or* o 1 corticosteroid course in the past 3 months; *or* o > 2 corticosteroid courses in the past year ≥ 1 week in duration • Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, SPT, or Screening DBPCFC • Lack of an available palatable vehicle food to which the subject is not allergic • Use of any therapeutic antibody (eg, omalizumab, mepolizumab, reslizumab, dupilumab, etc.) or any other immunomodulatory therapy excluding aeroallergen or venom immunotherapy, or corticosteroids within the past 6 months (Section 5.10) • Use of beta blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), calcium channel blockers, or tricyclic antidepressants (Section 5.10) • Pregnancy or lactation • Residing at the same address as another subject in this or any peanut OIT study • Developing DLS(s) in reaction to the placebo part of the Screening DBPCFC

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	• History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema, and chronic spontaneous urticaria or other physician-diagnosed physical urticaria syndrome • Allergy to oat • Hypersensitivity to epinephrine or any of the excipients in the IP • Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety • Inability to follow the protocol requirements • Patients being in any relationship or dependency with the sponsor and/or investigator • Subjects with a history of alcohol, medication or drug abuse
Treatment Description	Screening/baseline: Eligible subjects will undergo a DBPCFC at the end of the Screening portion of the study. The Screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines, progressing only up to a top challenge dose of 300 mg (444 mg cumulative) of peanut protein or placebo. Additionally, the DBPCFC will progress through the dose levels in a fixed sequence, without repeating any dose. Those subjects who have DLS at or before the 300 mg (444 mg cumulative) challenge dose of peanut protein (measured as 600 mg of peanut flour) will be randomized 3:1 to active treatment (AR101) or placebo. For each subject, a Blinded Evaluating Physician is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician (or Blinded Assessor) is not to be involved directly in the oversight of study product dosing or the assessment or management of AEs during the initial escalation, up-dosing, or maintenance phases of the study; nor should they be involved in the food challenge material preparation on the food challenge days. To the extent practicable, the same Blinded Evaluating Physician who determines DLS in the Screening DBPCFC should determine DLS in the Exit DBPCFC. Initial Escalation (2 consecutive days): Eligible subjects will be randomized and initiate OIT starting at a dose of 0.5 mg of IP, and then increase the dose incrementally at 20 to 30 minute intervals over the course of a single day to a maximum dose of 6 mg. Subjects who fail to tolerate at least a 3 mg dose will be considered escalation failures and will be discontinued from the study. Subjects who tolerate both the 3 mg and 6 mg doses of IP, or who tolerate the 3 mg but not the 6 mg dose, will undergo confirmatory testing of the tolerability of a 3 mg dose the following consecutive day (refer to Initial Escalation Schedule at end of synopsis). Subjects who tolerate this confirmatory dose will enter the Up-dosing Period. Subjects who do not tolerate this confirmatory dose will be discontinued. Therapy details are found in Section 3 and Section 6 of the protocol. Up-dosing: Subjects will receive daily oral dosing of peanut or placebo OIT for approximately 20 weeks, if up-dosing proceeds without holding at, or reducing, a dose level; up to 40 weeks, maximum. All escalation doses will be administered in a clinical research center (CRC) or other monitored setting (unless required by a specific institution, no distinction will be drawn between an investigational site, study center office, clinic, or CRC, provided the capability requirements for monitoring and emergency intervention are met by the facility). All up-dosing activities will be performed under direct observation. Therapy details are found in Section 3 and Section 6 of the protocol.

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	Maintenance: Those subjects who reach the target maintenance dose of 300 mg/d of IP will enter an approximately 12-week Maintenance Period of continued dosing at 300 mg/d weeks, which may be extended by up to an additional 4 weeks (for a maximum Maintenance Period duration of 16 weeks), or to a total Treatment Phase duration of 56 weeks, whichever occurs first. Exit DBPCFC: Following completion of the approximately 12-week Maintenance Period, subjects will undergo an Exit DBPCFC (to a cumulative maximum of 2043 mg of peanut protein). Subjects who complete 12 weeks of maintenance and fail to tolerate the Exit DBPCFC at 300 mg (443 mg cumulative) of peanut protein will not be eligible to enroll in the follow-on study ARC008. If ARC008 is not yet available at the study site, subjects may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is available. Subjects who do not tolerate 300 mg peanut protein at the Exit DBPCFC will not continue blinded study treatment in ARC010.
Study Procedures	The following procedures will be performed according to the scheduled visits tabulated in Appendix 1: • Informed consent (and assent, as age appropriate) • Inclusion/exclusion criteria • Review of Subject Eligibility Form • Medical/allergy history • Concomitant medications • Contraception review • Physical examination, including height and weight • Vital signs (blood pressure, pulse rate, body temperature) • Peak expiratory flow rate (PEFR) in subjects 6 years and older • Spirometry (FEV1) in subjects 6 years and older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (eg, active wheeze on physical examination) • Pregnancy test for females of childbearing potential (FOCBP) • Diet (food allergen) history • Blood draw (same venipuncture for all samples) to collect samples for: o Peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 assays o Complete blood cell count (CBC) o Optional blood sample for immune cell characterization assays (separate informed consent required) • SPT • IP administration at the CRC • Dispensing of IP for home dosing/return of unused IP • Assessment of dose tolerability to decide appropriateness of up-dosing or maintenance • DBPCFC, performed in accordance with PRACTALL guidelines, but with the protocol-specified modifications • Quality of life assessment using the FAQLQ and the FAIM questionnaire

Protocol ARC010 Synopsis	
Title	**AR101 TRIAL IN EUROPE MEASURING ORAL IMMUNOTHERAPY SUCCESS IN PEANUT ALLERGIC CHILDREN (ARTEMIS)**
	• Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma • Assessment of treatment satisfaction using TSQM-9, exit questionnaires, and palatability questions • Monitoring for dosing compliance • AE monitoring • Telephone follow-up • Treatment unblinding

Protocol ARC010 Synopsis

Initial Escalation Period, Day 1, Dosing Schedule

Day 1 Dose #	Study Product Dose (mg peanut protein or placebo)	Cumulative Study Product Dose (mg peanut protein or placebo)
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12

Doses will be delivered at 20- to 30-minute intervals.

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

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

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

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

Future dose escalations will occur every 2 weeks with the initial dose increase administered in the CRC.

Protocol ARC010 Synopsis

Up-dosing Period Dosing Schedule

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

Capsules and sachets (introduced during the Maintenance Period) will be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly. The 300 mg capsules will be used for at least the first 2 weeks of dosing during the 12-Week Maintenance Period.

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Abbreviation	Definition
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
AEI	adverse event of interest
ANCOVA	analysis of covariance
Aimmune	Aimmune Therapeutics, Inc.
ARB	angiotensin-receptor blockers
BA/BE	bioavailability/bioequivalence (studies)
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations (US)
CI	confidence interval
CODIT™	Characterized Oral Desensitization Immunotherapy™
CoFAR	Consortium of Food Allergy Research
CRC	clinical research center
CRF	case report form
CT-3	Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3, Article 7.4)
DBPCFC	double-blind, placebo-controlled food challenge
DLS	dose-limiting symptom(s)
DSMC	Data Safety Monitoring Committee
EAACI	European Academy of Allergy and Clinical Immunology
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EoE	eosinophilic esophagitis
ER	Emergency Room
FAIM	food allergy independent measure
FAQLQ	food allergy quality of life questionnaire
FDA	Food and Drug Administration (US)
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HPLC	high-performance liquid chromatography
ICH	International Council for Harmonisation

Abbreviation	Definition
ICON	International Consensus on (anaphylaxis)
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
kU_A/L	kilounits of antibody per liter
MedDRA	Medical Dictionary for Regulatory Activities
mg/d	milligrams per day
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NHLBI	National Heart, Lung, and Blood Institute
OIT	oral immunotherapy
PEESS	Pediatric Eosinophilic Esophagitis Symptom Scores
PEFR	peak expiratory flow rate
PP	Per Protocol
PRACTALL	PRACTical issues in ALLergology, Joint United States/European Union Initiative
SAE	serious adverse event
SAP	statistical analysis plan
SPT	skin prick test
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
VITAL	Voluntary Incidental Trace Allergen Labeling

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

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

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

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

Oral immunotherapy for peanut allergy has been widely studied in recent years and has demonstrated encouraging safety and efficacy results in early clinical trials. Additionally, beneficial immunologic changes have been shown to occur over time that would tend to indicate progression toward a clinical state of sustained desensitization with continued OIT (Oppenheimer et al, 1992; Secrist et al, 1995; Nelson et al, 1997; Kapsenberg et al, 1999; Lehrer et al, 1999; Frew, 2003; Bousquet, 2004; Wilson et al, 2005; Skripak et al, 2008; Jones et al, 2009; Narisety et al, 2009; Blumchen et al, 2010; Kim et al, 2011; Varshney et al, 2011).

The goal of Aimmune Therapeutics' **C**haracterized **O**ral **D**esensitization **I**mmuno**T**herapy (CODIT™) program for peanut allergy is to induce a state of clinically meaningful desensitization to peanut protein, where clinically meaningful desensitization is defined as the absence of moderate or severe allergic reaction following ingestion of modest, but potentially dangerous, amounts of peanut protein. In practical terms, this state of desensitization should be sufficient to protect a patient with peanut allergy in case of an accidental exposure to peanut while the patient is endeavoring to maintain a peanut-avoidant diet.

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

In the Phase 2 study ARC001, AR101 showed a clinically meaningful level of protection, defined as the ability to consume a maximum single dose of 300 mg and a cumulative dose of 443 mg in a double-blind, placebo-controlled food challenge (DBPCFC). The ability to tolerate this level of peanut protein would be expected to confer protection against a life-threatening event should a subject be accidentally exposed to peanut. This level of protection was achieved with daily dosing of AR101, a highly characterized, pharmaceutical-grade formulation of defatted peanut flour, when administered in a controlled OIT regimen. In Study ARC001, 79% of subjects who undertook the OIT regimen were able to achieve the target dose of 300 mg/d, after completing an Up-dosing Period that lasted, on average, approximately 20 weeks. Following just an additional 2 weeks of maintenance therapy at 300 mg/d, all subjects (ie, 23 of the 29 originally randomized to active treatment)

were able to tolerate at least 443 mg cumulative of peanut protein with no more than mild symptoms in a DBPCFC.

A peanut-allergic patient's threshold sensitivity to peanut can vary day-to-day by as much as 2 orders of magnitude (Glaumann et al, 2013). Also, accidental exposures of up to 1000 mg can occur from taking a single, inadvertent bite of a peanut-dense food, such as a peanut candy or a peanut butter sandwich. Therefore, in the current Phase 3 study, Aimmune has chosen to test if a significantly greater proportion of subjects undergoing OIT to a maintenance dose of 300 mg/d of peanut protein as AR101, as compared to placebo, will be able to tolerate at least 2043 mg cumulative of peanut protein with no more than mild symptoms in a DBPCFC after completing approximately 9 months of treatment.

1.2 Clinical Trials of AR101

Updated information on AR101 clinical trials is provided in the AR101 investigator brochure.

1.2.1 ARC001 Trial

ARC001 was a multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 (characterized peanut allergen) OIT in peanut-allergic children and adults (4 to 26 years of age). The study consisted of a Screening Period, including a Screening DBPCFC, an initial escalation period, an Up-dosing Period, and a Maintenance Period, followed by an Exit DBPCFC.

All eligible subjects underwent a DBPCFC of up to 100 mg (143 mg cumulative) of peanut protein or placebo during the Screening portion of the study. Those subjects who had dose-limiting symptoms (DLS) at or before the 100 mg (143 mg cumulative) challenge dose of peanut protein (measured as 200 mg of peanut flour) were randomized 1:1 to AR101 or placebo.

Subjects received daily oral dosing of AR101 or placebo OIT; all escalation doses occurred in a clinical research center (CRC) or other monitored setting and were administered under direct observation.

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

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

Efficacy Results:

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

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

At the time of the Exit DBPCFC, 100% of the 23 AR101 subjects undergoing the DBPCFC (Completer population) tolerated 443 mg (cumulative) as compared to 5 of the 26 (19%) placebo study completers ($p < 0.0001$ by Fisher's exact test).

At Exit DBPCFC, 18 of 29 (62%) AR101 subjects in the ITT population tolerated 600 mg (1043 mg cumulative) versus none of placebo subjects, resulting in a treatment difference of 62%. Post-hoc analysis by Fisher's exact test yielded statistical significance ($p < 0.0001$). In the Completer population, 18 of 23 (78%) AR101 subjects and no placebo subjects tolerated 600 mg at Exit DBPCFC.

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

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

For the key secondary endpoint of change from baseline in MTD of peanut protein at Exit DBPCFC analyzed using an analysis of covariance (ANCOVA) model, a treatment difference of 0.912 $\log_{10}$ mg ($p < 0.0001$) was observed with a change from baseline in MTD of 1.254 $\log_{10}$ mg for AR101 and 0.341 $\log_{10}$ mg for placebo. In terms of the ratio of MTD of

peanut protein at the Exit DBPCFC compared to baseline, AR101 subjects were able to tolerate 17.94 times as much peanut protein at the Exit DBPCFC compared to baseline, while placebo subjects were able to tolerate 2.19 times as much peanut protein at the Exit DBPCFC compared to baseline.

For the secondary endpoints of changes in peanut-specific IgE and peanut-specific IgG4 levels and related measures, the relative treatment effect was calculated as a ratio of 2 ratios (study exit result : baseline result in the AR101 group/study exit result : baseline result in the placebo group). The largest relative treatment effect, 4.756, was noted for peanut-specific IgG4, reflecting study exit values that were 5-times baseline in the AR101 group compared to levels that were nearly unchanged in the placebo group. The 95% CI around this relative treatment effect (3.271, 6.915) excluded the null value of 1.

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

Safety Results:

AR101 was generally well tolerated. The overall incidence of treatment-emergent adverse events (TEAEs) was 97% for the AR101 treatment group and 85% for the placebo group. One subject (3%) in the AR101 group experienced a treatment-emergent serious adverse event (SAE) of anaphylactic reaction related to treatment. One subject (4%) in the placebo group experienced an SAE of presyncope/anaphylaxis related to the peanut protein in the Exit DBPCFC (not investigational product [IP]). An additional subject experienced a pre-randomization, non-treatment-emergent SAE of anaphylactic reaction following the Screening DBPCFC. Four (14%) AR101 subjects discontinued due to adverse events (AEs), with either hypersensitivity (n = 3) or vomiting (n = 1). Two additional AR101 subjects discontinued due to treatment-related reasons that included gastrointestinal (GI) AEs, but not exclusively. No placebo subjects discontinued due to AEs. The most commonly occurring TEAE was hypersensitivity, which was reported in 73% of study subjects. The next most commonly reported TEAEs were pyrexia (16%), upper respiratory tract infection (13%), headache (11%), and vomiting (11%).

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

In summary, AR101 was safe, generally well tolerated, and statistically superior to placebo for reducing clinical reactivity to peanut allergen in peanut-allergic children and adolescents

to young adults. AR101 treatment significantly increased the probability of tolerating peanut allergen doses ≥ 300 mg and resulted in favorable changes in clinical markers of peanut allergen immunoreactivity, most notably peanut-specific IgG4 levels, as compared to placebo.

1.2.2 ARC003 Study

ARC003 (PALISADE) is an international, multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in a characterized desensitization OIT regimen in peanut-allergic individuals. The study consists of a Screening phase that includes a Screening DBPCFC, and a double-blind OIT treatment phase that includes an initial escalation period, an Up-dosing Period, and a Maintenance Period, followed by an Exit DBPCFC.

All eligible subjects are randomized in a 3:1 ratio to receive escalating doses of either AR101 or placebo. A DBPCFC will be performed for those subjects achieving the target dose of 300 mg/d and continuing to receive that dose throughout the Maintenance Period (approximately 24 weeks). Subjects who do not reach 300 mg/d will be considered escalation failures and non-responders for the primary analysis. Each subject will be unblinded when he/she completes the DBPCFC at the end of the approximately 24-week Maintenance Period and all major data queries for the subject have been resolved. Those who do not pass the DBPCFC at ≥ the 443-mg cumulative challenge dose level will be considered endpoint failures and non-responders for the primary analysis. The study is being monitored by an independent Data Safety Monitoring Committee (DSMC) that has met several times.

1.2.3 ARC004 Study

ARC004 is a randomized, controlled, open-label, multicentre study that will explore alternate dosing interval regimens during extended maintenance with AR101 in subjects completing Study ARC003. The primary objective is to confirm the safety profile of AR101 as measured by the incidence of AEs, including SAEs. The secondary objectives include confirmation of the efficacy of AR101 through reduction in clinical reactivity; evaluation of the efficacy and safety of different AR101 dosing schedules during extended maintenance therapy; evaluation of quality of life and treatment satisfaction during AR101 treatment; and evaluation of the long-term immunologic effects of AR101 treatment. This study is ongoing.

1.2.4 Open-label Follow-on Study, ARC008

The open-label follow-on study ARC008 is designed to accommodate subjects completing Aimmune-sponsored studies with AR101. The study is intended to demonstrate the safety of AR101 for an extended period (months to years) with the following objectives: unblinded expansion of the safety database for AR101, confirmation of the efficacy of OIT with AR101 up-dosed to a maintenance dose of 300 mg/d of peanut protein in the former ARC010 placebo population, and to provide an opportunity to the ARC010 trial participants to maintain the level of desensitization they may have achieved.

1.3 Rationale for Selection of Study Population

This study, ARC010 ARTEMIS, will enroll approximately 160 subjects 4 to 17 years of age with a history of allergy to peanut or peanut-containing foods. The sample size has been selected such that, in combination with the entire clinical experience with AR101 (eg, ARC001, ARC002, ARC003, ARC004), it is sufficient to assess the efficacy of AR101 in the relevant subject populations (Section 9.4).

All subjects enrolled must undergo a Screening DBPCFC to peanut, during which they need to react at or before the 300 mg (444 mg cumulative) dosing level of peanut protein (measured as 600 mg of peanut flour with approximately 50% protein content) in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) consensus guidelines (Sampson et al, 2012), regardless of how they were initially diagnosed as peanut allergic. In spite of the change in dose from 100 mg to 300 mg in ARC010, this should continue to select for the more sensitive half of the peanut-allergic population (Remington, 2013; Allen et al, 2014), according to a logistical regression analysis performed by the VITAL 2.0 study groups using food challenge data from multiple sources.

This ARC010 Phase 3 study (ARTEMIS) will focus on the age group most likely to be at greater risk from accidental exposure (ie, 4 to 17 years of age).

The lower age limit of 4 years was selected based on epidemiologic child-developmental considerations related to feeding behavior (Fallon et al, 1984; Cashdan, 1994; Farrow and Blisset, 2012; American Academy of Pediatrics, 2013), as well as practical clinical trial execution considerations and safety.

In the current study, subjects with severe or life-threatening episodes of anaphylaxis or anaphylactic shock will be excluded from enrolling only if they have had such an episode in the 60 days prior to the Screening DBPCFC, but will not otherwise be prohibited from entering the study. This is because peanut-allergic subjects who have had prior life-threatening episodes on exposure to peanut can be considered at high risk for another such episode, and hence, may be considered precisely the type of subjects who could benefit from desensitization therapy. The restriction of 60 days is applied for practical and safety reasons, as subjects who have had such a recent episode may be considered to have a potentially less favorable benefit-risk ratio for undergoing OIT; and such subjects may be reluctant to engage in the study.

1.4 Rationale for Selection of Investigational Product Regimen (Dose and Duration)

For this study, as well as the Phase 3 study ARC003, the dosing regimen used is predicated on the dosing regimen successfully used in the Phase 2 studies, ARC001 and ARC002. The ARC001 dosing regimen, in turn, was built on the work of the Consortium of Food Allergy Research (CoFAR) and its investigators. The basic structure of the dosing regimen consists of a single-day initial escalation at very low doses, followed by a build-up phase of dose escalations, with a single escalation occurring every 2 weeks, and then an maintenance phase at a fixed daily dose. This dosing regimen was shown to be well tolerated and effective in previous studies (Burks et al, 2012) and similarly was shown to be well tolerated and have clinically important activity in the Phase 2 studies ARC001 and ARC002.

The total duration of treatment in the current Phase 3 study will be approximately 9 months (approximately 5 months escalation and 3-4 months maintenance at 300 mg/d). The up-dosing regimen chosen for the current study was selected based on AR101's success in Phase 2.

The duration of maintenance therapy prior to testing for clinical efficacy by DBPCFC in the current study was similarly selected based on the outcome of the Phase 2 study. The clinical trials published to date for peanut OIT have had maintenance periods ranging from 1 to 7 months, and have demonstrated the ability to allow subjects to tolerate challenge doses ranging from 1.25 to 16.7 times their maintenance dose (Clark et al, 2009; Jones et al, 2009; Blumchen et al, 2010; Varshney et al, 2011; Anagnostou et al, 2014; Cronin et al, 2014; Vickery et al, 2016). The data from the ARC001 and ARC002 Phase 2 studies indicate that a clinically meaningful level of desensitization is achieved after up-dosing and just 2 weeks of daily maintenance dosing at 300 mg (with > 95% passing DBPCFC at a cumulative challenge dose of 443 mg of peanut protein and the majority passing at a 1043 mg cumulative challenge) and that extending maintenance dosing from 2 to 14 weeks appears to be associated with some improvement in the overall degree of desensitization. Accordingly, a blinded Maintenance Period of 3 months is considered sufficient to demonstrate efficacy and assess safety in this study. In addition, the ARC003 (PALISADE) Phase 3 confirmatory study will provide evidence of safety and efficacy after 6 months' maintenance therapy; the ARC010 (ARTEMIS) will provide complementary confirmatory evidence at 3 months' duration of maintenance, to evaluate whether clinically relevant desensitization in a significant proportion of subjects occurs at this shorter time frame.

The ability to convey to subjects that they are at a therapeutic level of desensitization in a reasonable timeframe is an important consideration. Thus, the total duration of blinded placebo therapy is limited to a maximum of 56 weeks in this study.

The data from the ARC001 and ARC002 studies, consistent with previously published studies, indicate that the use of a low-dose maintenance phase can provide a clinically meaningful level of desensitization that is considerably higher than the daily maintenance dose. Three studies in particular (Jones et al, 2009; Cronin et al, 2014; Vickery et al, 2016) have specifically reported that daily dosing with 300 mg of peanut protein will allow quantities of peanut protein ranging from 2.1 to 5 grams to be tolerated in an oral food challenge.

1.5 Rationale for the Doses Selected for the DBPCFC

The study DBPCFCs will be conducted in accordance with the recommended PRACTALL guidelines although the Screening DBPCFC will not exceed 300 mg (444 mg cumulative). This is to select subjects that are representative of approximately the more sensitive half of the peanut-allergic population (Section 1.3). The Exit DBPCFC will not go above a 1000 mg (2043 mg cumulative) dose to help ensure subject safety. Additionally, the DBPCFCs will progress through the dose levels in an unaltered sequence without repeating any dose to provide standardization of the amounts of peanut protein subjects are exposed to when being tested in the clinical trial setting.

The Exit DBPCFC will initially assess desensitization to 300 mg of peanut; to assess further desensitization, subjects will be administered 600 mg peanut protein, and in those shown to tolerate this exposure (1043 mg cumulative), an additional dose will be made with 1000 mg (2043 mg cumulative). This is equivalent to approximately 8 to 10 peanuts over the course of the day.

The ability to tolerate 1000 mg (2043 mg cumulative) will be assessed as the primary endpoint, and the ability to tolerate 600 mg (1043 mg cumulative) and 300 mg (443 mg cumulative) will be assessed as key secondary endpoints. As discussed in Section 1.1, all of these challenge dose levels are believed to represent amounts of peanut protein in excess of what might typically be encountered in an accidental ingestion of peanut.

1.6 Known and Potential Risks and Benefits to Human Participants

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

In subjects with peanut allergy, many OIT studies have been performed using procedures and dosing similar to those proposed in this study. In general, the safety profile has been very good across the studies, and based on those studies, approximately 80%, 15%, and < 1 % of the subjects are expected to have mild, moderate, or severe symptoms, respectively, during some point in their dosing with peanut OIT. It is important to note that essentially all AEs have been allergy related, predictable, and reversible. The major atypical AE from peanut OIT that has been reported in the literature is eosinophilic esophagitis (EoE), affecting an estimated 3 to 4% of OIT recipients (Lucendo et al, 2014), which is thought to be reversible upon dosing cessation.

The up-dosing and daily maintenance doses of peanut OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing, and/or shortness of breath in addition to severe anaphylaxis. The likelihood of a subject experiencing a severe allergic symptom is expected to be lessened by initiating dosing at extremely small amounts of AR101 and by up-dosing under observation in a clinical setting until the maintenance dose is achieved.

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

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

Please refer to the current edition of the AR101 Investigator's Brochure for further information regarding the safety profile, risks, and benefits of AR101.

2. OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

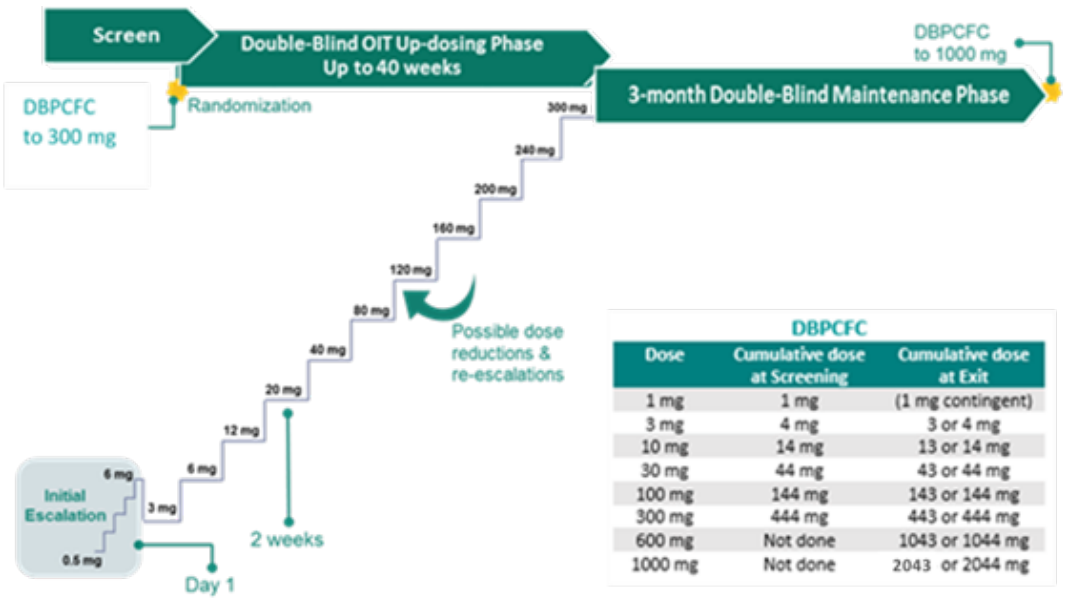
The secondary objectives are:

- To demonstrate the safety of AR101 as measured by the frequency of AEs, including SAEs.
- To evaluate the immunological effects of peanut OIT therapy.

3. STUDY DESIGN

ARC010 is a European, multicentre, randomized, double-blind, placebo-controlled study. The study design is illustrated in Figure 1.

Figure 1 Study Design



DBPCFC

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

3.1 Screening Period

Subjects 4 to 17 years of age must have a clinical history of allergy to peanut or peanut-containing foods, a serum IgE to peanut of ≥ 0.35 kU_A/L, and/or a SPT to peanut of ≥ 3 mm versus negative control at the time of Screening. Eligible subjects will undergo an initial DBPCFC at the end of the Screening Period (refer to Section 6.6.1). This DBPCFC

will include both a peanut challenge (defatted peanut flour) and a placebo challenge (artificially peanut-flavored oat flour) on separate days. The Screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines, with top challenge doses of 300 mg (444 mg cumulative) of peanut protein or placebo.

For each subject, a Blinded Evaluating Physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician, who is assessing and managing subject symptoms on the food challenge days, is not to be involved directly in the oversight of study product dosing or the assessment or management of AEs during the initial escalation, up-dosing, or maintenance phases of the study; nor should he or she be involved in the food challenge material preparation on the food challenge days. To the extent practicable, the same Blinded Evaluating Physician who determines DLS in the Screening DBPCFC should determine DLS in the Exit DBPCFC.

Those subjects who have DLS at or before the 300 mg (444 mg cumulative) challenge dose of peanut protein (measured as 600 mg of peanut flour) will be enrolled into the study. According to a logistical regression analysis performed by the VITAL 2.0 study group using food challenge data from multiple sources, this would select for the more sensitive portion of the peanut-allergic population (Remington, 2013; Allen et al, 2014). Those who successfully consume and tolerate a 300 mg (444 mg cumulative) dose of peanut protein during the Screening DBPCFC (ie, without manifesting DLS), will be considered screen failures and will not be randomized.

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

Approximately 160 subjects who pass Screening will be randomized 3:1 to either AR101 (active treatment) or placebo using a proprietary interactive response system.

3.2 Treatment Phase

The Treatment Phase comprises 3 periods:

- **Initial Escalation** (2 consecutive days) – Eligible subjects will be randomized and initiate OIT starting at a dose of 0.5 mg of IP, and then increase the dose incrementally at 20 to 30 minute intervals over the course of a single day to a maximum dose of 6 mg. Subjects who fail to tolerate at least a 3 mg dose will be considered escalation failures and will be discontinued from the study. Subjects who tolerate both the 3 mg and 6 mg doses of IP, or who tolerate the 3 mg but not the 6 mg dose, will undergo confirmatory testing of the tolerability of a 3 mg dose the following consecutive day (refer to Initial Escalation Schedule at end of synopsis). Subjects who tolerate this confirmatory dose will enter the Up-dosing Period. Subjects who do not tolerate this confirmatory dose will be discontinued. Therapy details are found in Section 3 and Section 6 of the protocol.

- **Up-dosing Period** – After the initial escalation period, subjects will report to the CRC every 2 weeks to escalate their OIT dose to an expected daily dose of 300 mg of peanut protein. This constitutes the Up-dosing Period. Subjects will receive daily oral dosing of peanut or placebo OIT for approximately 20 weeks, if up-dosing proceeds without holding at, or reducing, a dose level; up to 40 weeks, maximum. All escalation doses will be administered in a CRC or other monitored setting (unless required by a specific institution, no distinction will be drawn between an investigational site, study center office, clinic, or CRC, provided the capability requirements for monitoring and emergency intervention are met by the facility). All up-dosing activities will be performed under direct observation. Therapy details are found in Section 3 and Section 6 of the protocol.
- **Maintenance Period** – Those subjects who reach the target maintenance dose of 300 mg/d of IP will enter an approximately 12-week Maintenance Period of continued dosing at 300 mg/d, which may be extended by up to an additional 4 weeks (for a maximum Maintenance Period duration of 16 weeks), or to a total Treatment Phase duration of 56 weeks, whichever occurs first.

Treatment will be conducted in a double-blind fashion. The IP (AR101 or placebo) will be coded according to subject randomization number. The subjects and the investigational site personnel will be blinded to treatment assignment.

The dose-escalation schedule is described in detail in Table 1 and Table 2.

Table 1 Initial Dose Escalation Schedule

Initial Dose Escalation Schedule		
Day 1 Dose Number	**Investigational Product Dose, mg[a]**	**Cumulative Dose, mg**
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12

[a] All mg doses shown refer to milligrams of peanut protein or the equivalent placebo dose.
Doses will be delivered at 20 to 30 minute intervals under direct observation.
Capsules are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly and consumed.
Day 1: Subjects who are unable to tolerate a dose of 3 mg at the end of Day 1 will be considered escalation failures.
Subjects who tolerate ≥ 3 mg on Day 1 will return on Day 2 to receive a 3 mg single dose
Day 2: Subjects with either no symptoms or mild symptoms on Day 2 at 3 mg will start daily home dosing at 3 mg on Day 3.
Subjects with moderate or severe symptoms at 3 mg on either Day 1 or Day 2 will be considered escalation failures.

Subjects who reach and tolerate 300 mg/d will continue at that dose level for the duration of the Maintenance Period. The first Maintenance Visit occurs 2 weeks after the 300 mg Up-dosing Visit, with visits every 4 weeks thereafter. Any subject unable to achieve a dose of 300 mg/d of peanut protein by 40 weeks will not undergo the Exit DBPCFC.

Table 2 Up-dosing Schedule

Up-dosing Schedule			
Dose Number	**Investigational Product Dose, mg (peanut protein or placebo)**	**Interval (weeks)**	**Percent Increase from Previous Dose**
1	3	2 [a]	n/a
2	6	2	100
3	12	2	100
4	20	2	67
5	40	2	100
6	80	2	100
7	120	2	50
8	160	2	33
9	200	2	25
10	240	2	20
11	300	Enter Maintenance Period	25

[a] Interval includes Day 2 of Initial Escalation.

During the treatment period, the subjects will be monitored for the tolerability of IP, as described in Section 6.7.2 and Section 6.7.3.

If a subject discontinues therapy prematurely for any reason, the subject will be followed for safety and asked to return to the CRC 14 to 16 days following his or her last dose of IP to undergo an Early Discontinuation Visit (Section 6.4). In the event of ongoing AEs, subjects who have discontinued therapy should continue to be followed beyond the Early Discontinuation Visit until such time as the AE has resolved or is assessed to have reached a chronic stable state (a determination that may not be made sooner than 30 days after the Early Discontinuation Visit). Subjects who have GI AEs with prolonged disruption of dosing or who discontinue treatment due to GI AEs will have safety follow-up for 6 months or until chronic or recurrent GI symptoms resolve or stabilize, whichever is last (Section 7.3.3.2).

3.3 Exit DBPCFC

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

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

For each subject, a Blinded Evaluating Physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician, who is assessing and managing subject symptoms on the food challenge days, is not to be involved directly in the oversight of study product dosing or the assessment or management of AEs during the initial escalation, up-dosing, or maintenance phases of the study; nor should he or she be involved in the food challenge material preparation on the food challenge days. To the extent practicable, the same Blinded Evaluating Physician who determines DLS in the Screening DBPCFC should determine DLS in the Exit DBPCFC.

Each subject will be unblinded after he/she completes the DBPCFC, all major data queries to date (ie, queries that could influence allocation to 1 or another analysis population) for the subject have been resolved, and the follow-on study ARC008 is available at the study site. Subjects may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is available, unless specified otherwise (Section 3.4). To maintain the study blind overall, individual unblinding information should only be distributed to designated team members on a need-to-know basis as instructed by Aimmune.

Subjects who do not reach the target dose of 300 mg/d by Week 40 are not eligible for the Exit DBPCFC. These subjects will be unblinded once the database has been locked and unblinded.

3.4 Open-label Follow-on Study – ARC008

All placebo-treated subjects who complete ARC010 are eligible for rollover into the open-label follow-on study ARC008. In ARC008, placebo-treated subjects from ARC010 will undergo an escalation schedule, starting with the 0.5 mg dose and proceeding sequentially through the Up-dosingand Maintenance Periods in an open-label fashion identical to that for subjects who received AR101 in the ARC010 study. If subjects tolerate a daily dose of 300 mg during the Up-dosing Period, they will enter the Initial Maintenance Period. Once 24 weeks in the Initial Maintenance Period have been completed, subjects will then enter the Extended Maintenance Period and receive 300 mg/d until the end of the study. Subjects will be offered optional annual food challenges.

All AR101-treated subjects in ARC010 who pass the DBPCFC at the 443 mg cumulative dose level of peanut protein (ie, tolerate 443 mg cumulative dose with no more than mild symptoms) are eligible to proceed to ARC008. Subjects will receive 300 mg a day for the duration of the study, with visits every 3 months to the CRC. They will be offered the optional annual food challenges. Subjects who do not pass the DBPCFC at the 443 mg cumulative challenge dose level will not be eligible to enroll in ARC008.

If ARC008 is not yet available at the study site, subjects may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is available. Subjects who do not tolerate 300 mg peanut protein at the Exit DBPCFC will not continue blinded study treatment in ARC010.

3.5 Definition of End of the Study

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

3.6 Study Design Safety Considerations

The study design incorporates the following important safety considerations:

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

A DSMC will be established and will meet at time points defined in the DSMC charter to monitor the study for safety.

3.7 Primary Efficacy Endpoint

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

3.8 Secondary Endpoints

3.8.1 Secondary Efficacy Endpoints

3.8.1.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- The proportion of subjects who tolerate at least 600 mg as a single dose (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The proportion of subjects who tolerate at least 300 mg as a single dose (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The maximum severity of symptoms occurring following ingestion of peanut protein during the Exit DBPCFC

3.8.1.2 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are as follows:

- The MTD with no more than mild symptoms at Exit DBPCFC
- Change from baseline in MTD of peanut protein at Exit DBPCFC
- Use of epinephrine as a rescue medication at Exit DBPCFC and comparison to its use at Screening DBPCFC
- Changes in serum peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 levels
- Changes in peanut SPT mean wheal diameter
- Quality of life assessments using the food allergy quality of life questionnaire (FAQLQ) and the food allergy independent measure (FAIM; van der Velde et al, 2010) questionnaire

3.8.2 Exploratory Endpoints

- Treatment satisfaction assessment using the Treatment Satisfaction Questionnaire for Medication (the TSQM-9) and an exit questionnaire
- Assessment of palatability (taste and after-taste)

3.8.3 Safety Endpoints

- The safety of peanut OIT based on AEs and SAEs
- Use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods)
- Frequency and severity of anaphylaxis during OIT (Initial Escalation, Up-dosing, and Maintenance Periods), attributable to IP or accidental food exposure
- Frequency and severity of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the Maintenance Period, normalized for duration of treatment
- Frequency of accidental ingestion of peanut and other allergenic foods; frequency and severity of reactions resulting from accidental ingestion of peanut and other allergenic foods
- Frequency and severity of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs
- Assessment of asthma control using the 2007 National Heart, Lung, and Blood Institute (NHLBI) classification and the Asthma Control Test questionnaire in subjects with asthma

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Age 4 through 17 years (inclusive)
2. Clinical history of allergy to peanuts or peanut-containing foods

3. Serum IgE to peanut of ≥ 0.35 kUA/L (as determined by UniCAP™ within the past 12 months) and/or a peanut SPT wheal diameter ≥ 3 mm compared to control
4. Experience DLS at or before the 300 mg (444 mg cumulative) challenge dose of peanut protein (measured as 600 mg of peanut flour) on Screening DBPCFC conducted in accordance with PRACTALL guidelines
5. Written informed consent from subjects or parent/guardian for all subjects (or both parents when required by local authorities)
6. Written assent from minor subjects as appropriate (in accordance with local regulatory requirements)
7. Use of effective birth control by female subjects of childbearing potential (Section 7.10.3.2)

4.2 Exclusion Criteria

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

1. History of hemodynamically significant cardiovascular disease, including uncontrolled or inadequately controlled hypertension (Section 5.10)
2. History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of Screening DBPCFC
3. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of, becoming unstable or requiring a change in chronic therapeutic regimen including autoimmune diseases and malignancies (including malignancies occurring in the 5 years prior to Screening)
4. History of EoE, other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (eg, difficulty swallowing, food “getting stuck”), or recurrent GI symptoms of undiagnosed etiology
5. Current participation in any other interventional study and/or participation in another interventional clinical study within 30 days or 5 half-lives of the IP, whichever is longer, prior to randomization
6. Participation in, and having received active treatment in, any previous clinical study of AR101 CODIT
7. Currently receiving, or having received in the 5 years prior to Screening, any type of peanut or any other food immunotherapy clinical study (including subcutaneous, sublingual, oral, or epicutaneous)
8. Subject is in “build-up phase” of immunotherapy to another allergen (ie, has not reached maintenance dosing)
9. Severe asthma (2007 NHLBI Criteria Steps 5 or 6, Appendix 2)
10. Mild or moderate asthma (2007 NHLBI Criteria Steps 1 to 4), if uncontrolled or difficult to control as defined by any of the following:

- Forced expiratory volume in 1 second (FEV_1) < 80% of predicted, with or without controller medications (only for age 6 years or greater and able to do spirometry[1]); *or*
- Inhaled corticosteroids (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICS based on NHLBI dosing chart); *or*
- 1 hospitalization in the past year prior to Screening for asthma; *or*
- Emergency room (ER) visit for asthma within 6 months prior to Screening

11. History of high-dose corticosteroid use (eg, 1 to 2 mg/kg of prednisone or the equivalent for > 3 days) orally or parenterally in any of the following manners:
    - History of daily oral or parenteral corticosteroid dosing for > 1 month during the past year; *or*
    - 1 oral or parenteral corticosteroid course in the past 3 months; *or*
    - > 2 oral or parenteral corticosteroid courses in the past year ≥ 1 week in duration
12. Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, SPT, or Screening DBPCFC
13. Lack of an available palatable vehicle food to which the subject is not allergic
14. Use of any therapeutic antibody (eg, omalizumab, mepolizumab, reslizumab, dupilumab, etc.), or any other immunomodulatory therapy excluding aeroallergen or venom immunotherapy, or corticosteroids within the past 6 months (Section 5.10)
15. Use of beta blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), calcium channel blockers, or tricyclic antidepressants (Section 5.10)
16. Pregnancy or lactation
17. Residing at the same address as another subject in this or any peanut OIT study
18. Developing DLS in reaction to the placebo part of the Screening DBPCFC
19. History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema, and chronic spontaneous urticaria or other physician-diagnosed physical urticaria syndrome
20. Allergy to oat
21. Hypersensitivity to epinephrine or any of the excipients in the IP

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

22. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety
23. Inability to follow the protocol requirements
24. Patients being in any relationship or dependency with the sponsor and/or investigator
25. Subjects with a history of alcohol, medication or drug abuse

4.3 Premature Subject Termination from the Study

4.3.1 Criteria

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

Unless required for safety reasons (ie, medical treatment of an SAE), subjects eligible for an Exit DBPCFC will not be unblinded to their treatment assignment until after the subject completes the Exit DBPCFC and after all major data queries for the subject are resolved, and the follow-on study ARC008 is available at the study site. Subjects who are considered escalation failures will be unblinded once the trial database has been locked and treatment assignment unblinded.

Any subject will be prematurely terminated from additional study drug treatment and will be excluded from any further study procedures (with the exception of safety follow-up) for the following reasons:

1. Life-threatening symptoms (CoFAR Grade 4; refer to Table A4 in Appendix 4), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
2. Severe allergic hypersensitivity symptoms (CoFAR Grade 3; refer to 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 trial under close supervision, if both the Investigator and the medical monitor deem it appropriately safe to do so
3. Pregnancy
4. Non-adherence (non-compliance) with study product dosing, as indicated by missing > 7 consecutive dosing days on any 1 occasion, or 3 consecutive dosing days on 3 or more occasions during the Up-dosing Period, as this could constitute a potential safety issue

5. Medically indicated circumstances (eg, as part of the treatment for intercurrent AEs) that require missed study product dosing for >14 consecutive days, except for the voluntary 30-day hiatus for AEs occurring at or before the 20-mg dose
6. The subject elects to withdraw consent from all future study activities, including follow-up.
7. The subject is lost to follow-up (ie, no further follow-up is possible because attempts to re-establish contact with the subject have failed).
8. The subject's continued participation in the study is assessed by the investigator to constitute a threat to the safety of the subject or the safe conduct of the study.
9. The subject dies.
10. Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma)
11. Started on ARB, ACE inhibitors, beta blockers, or other prohibited medications, with no alternative medications available per the prescribing doctor
12. The subject develops biopsy-documented EoE

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

4.3.2 Follow-up of Subjects Who Discontinue Treatment

If a subject discontinues therapy for any reason, the subject will be followed for safety and asked to return to the CRC for an Early Discontinuation Visit 14 to 16 days after their last dose of IP. To the extent possible, subjects will be monitored for safety until they come back for their Early Discontinuation Visit.

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

Subjects who have GI AEs with prolonged disruption of dosing or who discontinue treatment due wholly or in part to GI AEs will have safety follow-up for 6 months or until chronic or recurrent GI symptoms resolve or stabilize, whichever is last, and be instructed to complete the Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS^{TM} v2.0) questionnaire (Franciosi et al, 2011) at the time of treatment discontinuation and monthly for 6 months (Section 7.3.3.2). Additional instructions for the follow-up of subjects who discontinue treatment due wholly or in part to GI AEs are provided in Section 7.3.3.2.

5. STUDY TREATMENT

5.1 Formulation, Packaging, and Labeling

The active IP, AR101, is characterized peanut allergen in the form of peanut flour, formulated with a bulking agent and a flow agent in pre-measured graduated doses,

comprising capsules containing 0.5, 1, 10, 20, and 100 mg each of peanut protein. AR101 is characterized by its high-performance liquid chromatography (HPLC) fingerprint and by specific enzyme-linked immunosorbent assays (ELISAs) performed against key allergenic proteins to demonstrate stability and lot-to-lot comparability. Placebos, containing only excipients that are color-matched to the peanut flour, will be provided as matching capsules, identical to the active capsules. For maintenance dosing, 300 mg of peanut protein are provided in sealed, foil-laminate sachets (1 sachet/day). Matching placebo-containing sachets are also provided.

Capsules containing IP will be provided in blister cards assembled into dosing kits. Each individual blister of a blister card will contain a single day's dose of IP; each kit will contain 21 daily doses at a given dose level, enough to supply 2 weeks of dosing plus a 7-day overage to accommodate potential visit scheduling issues (Section 3).

IP will be distributed to subjects/subjects' parents or guardians by study site personnel.

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

5.2 Preparation, Administration, and Dosage

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

In exceptional circumstances when a subject is unable to return to the CRC 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.

Procedures for preparation and administration of doses given in clinic or at home are the same. Dose preparation is to be completed by the subject or supervising adult, as age-appropriate. (For in-clinic dosing, dose preparation may be performed by clinic staff or by parent/subject under the direct supervision of clinic staff for the purpose of teaching and reinforcing training.) The capsules should be pulled apart, and gently rolled between finger and thumb, followed by a light tap to the end of each half of the capsule to ensure full

delivery of contents. The contents of the capsules or the sachets are to be mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other palatable, age-appropriate food. Care must be taken not to inhale the powder as this could provoke worsening of asthma or induce an allergic reaction.

Investigational product may not be added to food heated above room temperature before consumption. The vehicle food must be one to which the subject is not additionally allergic. The volume of the vehicle food should be such that the entire dose can be consumed in a few spoonfuls.

The IP should be consumed as promptly after mixing as practicable. If preparing a new dose is not feasible, the study product may be stored for up to 24 hours under conditions appropriate for the food matrix in which the IP was prepared. If there is a delay of more than 24 hours in consumption, the IP is to be discarded and a new IP dose mixed and consumed. It is recommended that each dose of IP be taken at a consistent time (within a 4-hour period) each day. A target interval of at least 8 hours should pass between doses.

Except for in-clinic dosing, the daily home dose should be taken as part of a meal. Dosing at the evening meal is recommended to permit children to be observed and supervised in the home setting by their parents or guardians for several hours after dosing.

Subjects are to be cautioned against activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths within 3 hours after dosing). Dosing should also not occur within 2 hours of bedtime. Additionally, if a subject has been engaged in strenuous exercise prior to dosing, dosing should be delayed until signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.

Except as may be necessary in the course of treating an AE (Section 6.7), it is crucial that subjects take their dose every day, after they commence dosing on Day 1. No attempt should be made to make up for a missed dose if greater than 6 hours have elapsed since usual time of dosing.

5.3 Investigational Product Accountability

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

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

5.4 Assessment of Compliance with Study Treatment and Monitoring

Families will document daily dosing and any reaction to at-home dosing using diary logs. Central monitoring of dosing compliance will be performed by comparing returned unused IP against the daily dosing records.

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

5.5 Modification of Study Treatment

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

5.6 Concomitant Medications

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

5.7 Prophylactic Medications

None.

Although symptomatic treatments for chronic/recurrent AEs are permitted (eg, H1 or H2 histamine blockers, proton pump inhibitors, or inhaled 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.

5.8 Rescue Medications for Acute Allergic Reactions

Treatment of individual acute allergic reactions during Study ARC010 should be with either an antihistamine and/or epinephrine, along with IV fluids, beta-adrenergic agonist (eg, salbutamol), oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely already to have an epinephrine auto-injection device, but for those who do not, an epinephrine auto-injection device will be provided. The expiry dates for the epinephrine auto-injectors will be tracked at the investigational site and subject/families resupplied as necessary. Study staff must document in each subject's medical record that the subject and parent/guardian have an unexpired epinephrine auto-injection device and have been trained in its proper usage including injection technique.

5.9 Symptomatic Treatment for Chronic and/or Recurrent Adverse Events

Symptomatic treatment for chronic/recurrent AEs is permitted (with the exception of prohibited medications, Section 5.10), but should be used to supplement dose reduction, not substitute for it. It is advised that an attempt to withdraw symptomatic therapy be made prior to dose re-escalation. If unsuccessful, symptomatic therapy may be resumed and dose escalation may proceed with the symptomatic therapy in place. However, any therapy instituted for treatment of symptoms (AEs) related to IP must be withdrawn by 4 weeks prior to Exit DBPCFC. If a subject is unable to tolerate a daily maintenance of 300 mg of IP for at least the last 4 weeks of dosing prior to Exit DBPCFC free of any symptomatic therapy that was initiated during the course of OIT, the subject will be considered a "maintenance failure non-responder".

5.10 Prohibited Medications

1. Therapeutic antibodies such as, but not exclusive to omalizumab (Xolair®), mepolizumab (Nucala®), reslizumab (Cinqair®), dupilumab (Dupixent®), last used within 6 months of Screening
2. Systemic (oral) corticosteroids used for any greater duration than a total of 3 consecutive weeks throughout the study. If used, subjects must not be up-dosed during the 3 days after ceasing the administration of oral steroids
3. Beta blockers (oral)
4. ACE inhibitors
5. ARB
6. Calcium channel blockers
7. Tricyclic antidepressants

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

Immunomodulatory (including immunosuppressive) medications constitute another class of drugs whose use during the course of the study is generally prohibited. It is beyond the scope of this protocol to list all immunomodulatory drugs; broadly, these include drugs to treat or

prevent transplant rejection, autoimmune disease, and certain neoplasias. Examples include cyclosporine, tacrolimus, anti-tumor necrosis alpha drugs, anti-IgE drugs, and anti-IL-5 (or IL-5 receptor targeted drugs). If an investigator contemplates the use of a potentially immunomodulatory drug during the course of the study, the investigator should discuss this with one of the study's medical monitors prior to initiating use of the drug.

6. STUDY PROCEDURES

6.1 Enrollment and Randomization

Subjects will have an initial Screening DBPCFC consisting of both a peanut challenge and a placebo challenge before randomization. The peanut and placebo challenges will be conducted in a double-blind fashion, using foodstuffs provided by an unblinded site pharmacist, nutritionist, or study coordinator. Those subjects reacting to ≤ 300 mg of peanut protein (≤ 444 mg cumulative) will be randomized in a 3:1 ratio to AR101 or placebo. Those able to successfully consume the 300 mg (444 mg cumulative) top challenge dose of peanut protein during their DBPCFC (ie, do not develop DLS), will not be eligible for the study. In addition, those reacting (experiencing DLS) to ≤ 300 mg of the placebo challenge will not be eligible for the study. Because of the requirement for the peanut DBPCFC, the Screening Period will need to be conducted over more than 1 day.

Randomization will be performed using a proprietary interactive response system on Day 1 of the Initial Escalation Period.

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

6.2 Screening Period

Prior to the commencement of any study-related procedures, the investigator, or designee, must obtain written informed consent/assent from the subject and parent/guardian (as applicable), as described in Section 11.2. The date of signing the consent/assent form is the first day of the Screening Period.

All Screening procedures must be completed no later than 28 days from the signing of the consent/assent form.

Screening will include the following assessments/procedures:

- Informed consent and assent, as age appropriate
- Inclusion/exclusion criteria review
- Review of Subject Eligibility Form
- Medical and allergy history review
- Diet (food allergen exposure) history review
- Concomitant medication review
- Completion of the FAQLQ and FAIM questionnaires anytime during Screening before the DBPCFC

- In subjects with asthma: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire
- Complete physical examination, including weight and height
- Vital sign measurement (BP, pulse rate, body temperature). In addition to initial Screening vital sign measurements, vital sign measurements are required just prior to each DBPCFC challenge dose or at 15 to 20-minute intervals post-dose, if the between challenge dosing interval is longer
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (forced expiratory volume in 1 second [FEV_1]), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (eg, active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Serum pregnancy test for females of childbearing potential (pregnancy test result must be available prior to the DBPCFC)
- Blood draw (same venipuncture for all samples), at any time during Screening prior to the DBPCFC, to collect samples for:
  - Peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 assays
  - Complete blood cell count (CBC)
  - Optional blood sample for immune cell characterization assays

  The amount of blood to be taken in total for all tests (required immunoglobulin and CBC and optional immune cell characterization assays) will be included in the manual of procedures and not exceed a total volume of 2.5 mL/kg, to a maximum total of 70 mL on any study day. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. Multiple attempts to obtain blood, and repeat samples can be collected where necessary for damaged samples or safety reasons.
- SPT to peanut extract
- Confirmation subject or subject's parent or guardian has an unexpired epinephrine auto-injector prior to leaving the clinic following Day 1 of the DBPCFC

- DBPCFC conducted in accordance with PRACTALL guidelines, with assessments made by a Blinded Evaluating Physician (Blinded Assessor), as described in Section 6.6.
- Monitoring for AEs, including allergic symptoms (Section 6.7) commences from the time the consent/assent form is signed
- Subjects will be instructed to continue to follow a peanut-avoidant diet for the duration of the study.
- Subjects and parents or guardians will additionally receive teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):
  - Recognition of an allergic reaction and of the symptoms of anaphylaxis
  - When and how to administer epinephrine via auto-injector
  - Requirement to go to nearest emergency facility following use of epinephrine auto-injector
  - Ways to minimize the risk of accidental exposure to peanut in, and outside of, the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)

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

6.3 Study Treatment Visits

6.3.1 Confirmation of Eligibility and Randomization

At the end of the Screening DBPCFC assessment, the food challenge materials will be unblinded to establish whether any DLS demonstrated by the subject were a result of the peanut or the placebo food challenge material. If DLS are established to have occurred as a result of (only) the peanut food challenge material the following steps will be taken:

- Assessment that the subject still meets all eligibility criteria – a Subject Eligibility Form, which documents subject eligibility, is completed and sent to the medical monitor for review
- Medical monitor will review the Eligibility Form and confirm whether the subject is eligible to proceed to randomization (within 72 hours of receipt of the completed Eligibility Form), if applicable.
- Subject's Initial Escalation Day 1 visit is confirmed and should occur such that Initial Escalation Day 1 is not later than 29 days following the signing of the consent/assent form. Any deviation from this window must be discussed with and agreed by the medical monitor.
- Before randomization, inclusion and exclusion criteria are reviewed again to confirm the subject remains eligible for the study.

- The randomization day and Initial Escalation Day 1 should ideally be the same date. The investigator, or designee, will randomize the subject in the interactive response system on Initial Escalation Day 1 prior to the first dose of IP. The exception to this is if it is not logistically feasible to randomize a subject and commence initial escalation dosing on the same day; in this situation the site may randomize a subject in the interactive response system shortly (maximum 3 days) prior to Initial Escalation Day 1.

6.3.2 Initial Escalation Period

6.3.2.1 Day 1

The Initial Escalation Day 1 visit should occur within 10 days of the Screening DBPCFC Day 2 and must occur within 6 weeks (preferably by Day 29) following signing of the consent/assent form. If the Initial Escalation is not started in this time frame, written approval to rescreen the subject and/or to waive any of the Screening procedures must be obtained from the sponsor's medical monitor.

A physician must be available at all times during the CRC dosing visits. Subjects must be free from active wheezing or a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to initiating IP dose escalation. Additionally, subjects must be fully recovered (ie, back to their baseline state of health), from any preceding illness for at least 3 days, depending on the investigator-determined severity of the illness.

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

Day 1 visit in the CRC:

- Concomitant medication update
- Complete physical examination, including weight
- Diet (food allergen exposure) history update
- Pre-dose vital sign measurement (BP, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time of day for each visit assessment (eg, morning, afternoon, evening).
- Administration of IP (AR101 or matching placebo) at the site, with dosing beginning at 0.5 mg and progressing in graduated doses (if tolerated) of 1, 1.5, 3, and 6 mg. Following the first dose, subsequent doses will be delivered at 20 to 30 minute intervals. The schedule for initial day dose escalation is shown in Appendix 1.
- Post-dose vital sign measurements (BP, pulse rate) at the following times:
  - Within 15 to 30 minutes post-dose,
  - At 30 minute intervals thereafter and for the duration of the post-dose observation period.

- Monitoring for AEs, including allergic symptoms (below and Section 6.7 and Section 7.2)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

Subjects may have clear liquids or flavored gelatin during the day of the initial day escalation procedure while they are being given the desensitization doses.

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

- If Day 1 dose escalation is completed with no symptoms detected after 90 minutes of post-dose observation, the subject may be sent home from the CRC.
- If the subject exhibited **mild symptoms**, the duration of the observation period should be extended beyond 90 minutes, if applicable, so that the subject is observed for a minimum of 1 hour after resolution of the symptoms. Subject can continue in the study.
- For **moderate symptoms**, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. Subject is to be discontinued as an escalation failure.
- For **severe symptoms**, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate. Subject is to be discontinued as an escalation failure.
- Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status, stage 3 anaphylaxis defined in Appendix 3, or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the medical monitor and discontinued from the study.
- If DLS occur at or before the 3 mg single dose, there will be no further dosing of IP. The subject will be asked to return to the CRC 14 to 16 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.4). The subject will continue to be monitored for safety until the Early Discontinuation Visit is completed or any ongoing AEs are resolved, whichever comes first.
- If no DLS occur during Day 1 dose escalation, or if DLS occur only with the 6 mg single dose, the subject is to return to the CRC on Day 2 to confirm the tolerability of a single 3 mg dose of IP.

6.3.2.2 Day 2

On Day 2, the next consecutive day following Day 1, a single confirmatory 3 mg dose will be administered under medical supervision in the CRC. The only exception to Day 2

immediately following Day 1 is when unforeseen circumstances (eg, an intercurrent illness) create a safety risk to provide the next dose, consistent with the rules for missed doses (Section 6.8). Should this occur, the investigator should discuss the case with the medical monitor prior to administering the next dose.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to continuing with Day 2 of the initial dose escalation.

The following assessments/procedures will be performed:

- Concomitant medication update
- Symptom-directed physical examination
- Diet (food allergen exposure) history update
- Pre-dose vital sign measurement (BP, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should, as far as possible, be measured at the same time of day at each visit (eg, morning, afternoon, evening)
- Oral administration of a single 3 mg dose of IP
- Post-dose vital sign measurements (BP, pulse rate) at the following times:
  - Within 15 to 30 minutes post-dose,
  - At 30-minute intervals thereafter and for the duration of the post-dose observation period.
- Monitoring for AEs, including allergic symptoms (Section 6.7)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

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

- If Day 2 dosing is completed with no symptoms detected after 90 minutes of post-dose observation, the subject may be sent home from the CRC.
- If the subject exhibited **mild symptoms**, the duration of the observation period should be extended beyond 90 minutes, if applicable, so that the subject is observed for a minimum of 1 hour after resolution of the symptoms. Subject can continue in the study.
- For **moderate symptoms**, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. Subject is to be discontinued as an escalation failure.

- For **severe symptoms**, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate. Subject is to be discontinued as an escalation failure
- Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status (stage 3 anaphylaxis defined in Appendix 3), or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the medical monitor and discontinued from the study.
- If DLSs occur on Day 2, there will be no further dosing. The subject will be asked to return to the CRC 14 to 16 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.4). The subject will continue to be monitored for safety until the Early Discontinuation Visit is completed or any ongoing AEs are resolved, whichever comes first.
- Those subjects who tolerate the single 3 mg dose of IP on Day 2 will be dispensed a 2-week supply of IP at the 3 mg/d dose level. They will be instructed to continue daily oral dosing at home, starting the following day (Day 3), and to continue daily home dosing at that dose level for 2 weeks until next escalation.
- Subjects and parents/guardians will be educated on home dosing instructions per Section 5.2.

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

6.3.3 Up-dosing Period

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

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

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

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

6.3.3.1 Up-dosing Visits

The following assessments/procedures are scheduled for each Up-dosing Visit in the CRC:

- Concomitant medication review
- Contraception review
- Diet (food allergen exposure) history update
- Return unused IP
- Symptom-directed physical examination
- Pre-dose vital sign measurement (BP, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time of day for each visit assessment (eg, morning, afternoon, evening)
- IP administration under observation in the clinic
- Post-dose vital sign measurements (BP, pulse rate) at the following times:
  - Within 15 to 30 minutes post-dose,
  - At 30-minute intervals thereafter, if the time between doses is extended, and for the duration of the post-dose observation period.
- Provide subject with IP for daily dosing until next visit
- Monitoring for dosing compliance
- Monitoring for AEs, including allergic symptoms (below and Section 6.7 and Section 7.2) and review of symptoms reported in subject diary
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

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

- If up-dosing is completed with no symptoms detected after 90 minutes of post-dose observation, the subject may be sent home from the CRC.
- If the subject exhibited **mild symptoms**, the duration of the observation period should be extended beyond 90 minutes, if applicable, so that the subject is observed for a minimum of 1 hour after resolution of the symptoms.
- For **moderate symptoms**, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms.
- For **severe symptoms**, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

- Any subject deemed to have **severe symptoms** that include hypoxia, hypotension, or change in mental status (stage 3 anaphylaxis defined in Appendix 3), or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the medical monitor and discontinued from the study.
- On the day following in-clinic up-dosing, the site is to make telephone contact with the subject/subject's parent or guardian to enquire if any AEs (including allergic symptoms) occurred subsequent to the subject leaving the clinic, and to provide assistance in the recording of any such events in the diary.
- A dose escalation attempt may be postponed 1 to 2 weeks if, in the clinical judgment of the investigator, the current dose level has not been sufficiently well tolerated to proceed to the next dose level.
- If an investigator suspects that a subject has not tolerated, or is not tolerating, his or her current dose level, the investigator should have the subject return to the clinic to determine whether a dose reduction is warranted, and if so, the magnitude of the reduction. The investigator may also decide to maintain the current dose or to withhold dosing. Guidelines for setting the new, lower dose are outlined in Section 6.7.5, with the dose adjustment depending on the severity of the dose-related symptoms.
- Subjects who require dose reduction during a 2-week dosing period will have their escalation schedule reset, as necessary, to maintain the new dose level for a 2-week period prior to attempting to re-escalate.
- Following a dose reduction, it is advised that an escalation attempt be made by 4 weeks, unless escalation is to be delayed further due to administration of epinephrine, as defined in Section 6.7. Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced at least 2 weeks apart, will result in the cessation of dosing. The subject will be asked to return to the CRC 14 to 16 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.4) and is to be followed for safety in the interim.
- For symptoms occurring during the Maintenance Period, the same study dosing rules and guidelines that apply for the Up-dosing Period will also apply.

6.3.3.2 80 mg Up-dosing Visit

The 80 mg Up-dosing Visit is the approximate midpoint of the Up-dosing Period. At the 80 mg Up-dosing Visit the following procedures are to be performed in addition to those performed at the other Up-dosing Visits:

- Complete physical examination, including height and weight
- In subjects with asthma: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire
- Urine pregnancy test for females of childbearing potential

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

6.3.3.3 300 mg Up-dosing Visit

At this visit the following procedures are to be performed in addition to those performed at the Up-dosing Visits:

- Complete physical examination, including height and weight
- In subjects with asthma: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire
- Urine pregnancy test for females of childbearing potential
- Blood draw (same venipuncture for all samples) to collect samples for:
  - Peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 assays
  - CBC
  - Optional blood sample for immune cell characterization assays

  The amount of blood to be taken in total for all tests (required immunoglobulin and CBC and optional immune cell characterization assays) will be included in the manual of procedures and will not exceed a total volume of 2.5 mL/kg, to a maximum total of 70 mL on any study day. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. Multiple attempts to obtain blood, and repeat samples can be collected where necessary for damaged samples or safety reasons.

- SPT to peanut extract
- Review home dosing instructions
- Review with subjects and parents or guardians teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):

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

6.3.4 Maintenance Period

The first Maintenance Visit will occur 2 weeks after the start of dosing at 300 mg/d; thereafter, Maintenance Visits will occur approximately every 4 weeks.

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

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

- Concomitant medication review
- Contraception review
- Diet (food allergen exposure) history update
- Return unused IP to the clinic at each visit
- Symptom-directed physical examination
- Pre-dose vital sign measurement (BP, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time of day for each visit assessment (eg, morning, afternoon, evening).
- IP administration under observation in the clinic
- Post-dose vital sign measurements (BP, pulse rate) at the following times:
  - Within 15 to 30 minutes post-dose;
  - At 30 minute intervals thereafter, and for the duration of the post-dose observation period is extended beyond 30 minutes.
- Provide subject with take home sachets (or capsules, as appropriate) for daily dosing until next visit
- Monitoring for dosing compliance
- Monitoring for AEs, including allergic symptoms (below and Section 6.7 and Section 7.2)
- Review home dosing instructions (only at first visit in Maintenance Period)

- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

In the event that dose reduction from the stable dose of 300 mg/d is required during the last weeks of the planned 12-week Maintenance Period, the Maintenance Period may be extended on an individual basis up to an additional 4 weeks (to a maximum of 16 weeks) or to a maximum study duration of 56 weeks, whichever is shorter. The Exit DBPCFC must be performed by Study Week 56. Additionally, subjects must maintain a dose of 300 mg/d for at least the last 4 consecutive weeks of the Maintenance Period without the use of symptomatic therapy to qualify for the Exit DBPCFC. Failure to do so will result in the subject being discontinued from the study.

If dosing is discontinued, the subject will be asked to return to the CRC 14 to 16 days following his or her last dose of AR101 to undergo an Early Discontinuation Visit (Section 6.4).

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

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

6.3.5 Unscheduled Visits / Unscheduled Blood Draws

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

Additionally, if a subject or subject's parent/guardian declares his or her intention to discontinue IP dosing, whether at a scheduled visit or an unscheduled visit, a blood draw should be performed for CBC and immunoglobulin assays, and, for subjects who provided prior consent/assent, for optional exploratory immune cell characterization samples. If a blood draw is performed at this time, it will take the place of the Early Discontinuation Visit blood draw.

6.4 Early Discontinuation Visit

Subjects who fail initial escalation or up-dosing, or who prematurely discontinue treatment, will return to the site for an Early Discontinuation Visit. An Early Discontinuation Visit is to occur 14 to 16 days after the last dose of IP.

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

- Concomitant medication review
- Diet (food allergen) history update
- Completion of the palatability questions
- Completion of the FAQLQ and FAIM questionnaires

- Completion of the TSQM-9 and exit questionnaires
- In subjects with asthma: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire
- Complete or symptom-directed physical examination, including weight and height
- Vital signs (BP, pulse rate, body temperature); if DBPCFC is to be conducted, these vital sign measurements should be taken shortly before the first challenge dose
- PEFR, performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted. The attempt must be documented, and a clinical assessment is required. Airflow assessment should be measured at the same time of day as for prior visit assessments (eg, morning, afternoon, evening).
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (eg, active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry.
- Urine pregnancy test for females of childbearing potential
- Blood draw (same venipuncture for all samples) to collect samples for:
  - Peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 assays
  - CBC
  - Optional blood sample for immune cell characterization assays

  The amount of blood to be taken for all tests (required immunoglobulin and CBC and optional immune cell characterization assays) will be included in the manual of procedures and not exceed a total volume of 2.5 mL/kg, to a maximum total of 70 mL on any study day. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. (For subjects who discontinue early, the blood draw at the Early Discontinuation Visit can be foregone if it was performed at the time that dosing with IP ceased.) Multiple attempts to obtain blood, and repeat samples can be collected where necessary for damaged samples or safety reasons.
- SPT to peanut extract
- Monitoring for AEs, including allergic symptoms (Section 6.7 and Section 7.2)

Study subjects who discontinue the study before the scheduled Exit Visit will remain blinded until the end of the study (final database lock and unblinding), unless emergency unblinding is necessary (Section 6.12.3).

6.5 Exit Visit

Subjects who tolerate 300 mg/d and are maintained at this dose for approximately 12 weeks (up to a maximum of 16 weeks, see Section 6.11) will return to the clinic for an Exit Visit.

The following procedures will be performed at the Exit Visit:

- Concomitant medication review
- Diet (food allergen) history update
- Completion of the palatability questions before the Exit DBPCFC
- Completion of the FAQLQ and FAIM questionnaires after the completion of the Exit DBPCFC and unblinding of each subject
- Completion of the TSQM-9 and exit questionnaires after the completion of the Exit DBPCFC and unblinding of each subject
- In subjects with asthma: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire
- Complete physical examination, including weight and height
- Vital signs (BP, pulse rate, body temperature) taken shortly before the first DBPCFC dose
- PEFR, performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted. The attempt must be documented, and a clinical assessment is required. Airflow assessment should be measured at the same time of day as for prior visit assessments (eg, morning, afternoon, evening).
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (eg, active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry.
- Urine pregnancy test for females of childbearing potential
- Blood draw (same venipuncture for all samples), prior to DBPCFC, to collect samples for:
  - Peanut- and peanut component-specific IgE, total IgE, and peanut-specific IgG4 assays
  - CBC
  - Optional blood sample for immune cell characterization assays

  The amount of blood to be taken for all tests (required immunoglobulin and CBC and optional immune cell characterization assays) will be included in the manual of procedures and not exceed a total volume of 2.5 mL/kg, to a maximum total of 70 mL

on any study day. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. Multiple attempts to obtain blood, and repeat samples can be collected where necessary for damaged samples or safety reasons.

- SPT to peanut extract
- Monitoring for AEs, including allergic symptoms (Section 6.7 and Section 7.2)

In addition to the procedures listed above, eligible subjects will have an Exit DBPCFC performed. Eligible subjects are those who tolerate 300 mg/d and are maintained at this dose for the approximately 12-week Maintenance Period. Subjects may have a dose reduction but must be on a dose of 300 mg/d without symptomatic therapy for the 4 weeks immediately preceding the Exit DBPCFC. The Exit DBPCFC is to be conducted in accordance with PRACTALL guidelines, with the protocol-specified modifications, as described in Section 6.6.2.

Each subject participating in the study will be unblinded when he/she completes the Exit Visit procedures (including the Exit DBPCFC for eligible subjects), all major data queries (ie, queries that could influence allocation to 1 or another analysis population) for the subject have been resolved, and the follow-on study ARC008 is available at the study site (refer to Section 3.3). If the open-label follow-on study ARC008 is not yet available at the study site, the subject may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is available. Subjects who complete 12 weeks of maintenance and who do not tolerate 300 mg peanut protein at the Exit DBPCFC will not continue blinded study treatment in ARC010.

All AR101-treated subjects who pass the Exit DBPCFC at the 443 mg cumulative dose level of peanut protein (ie, tolerate 443 mg cumulative dose with no more than mild symptoms) are eligible to proceed to ARC008. All placebo-treated subjects who complete the study are eligible for rollover into ARC008.

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

The DBPCFC is to be conducted as 2 challenges, each part on a separate day, using a placebo (artificially peanut-flavored oat flour) for 1 challenge and peanut (as defatted peanut flour) for the other. The 2 challenge days should be scheduled as closely together as practicable (allowing the washout period for antihistamines) and should not be scheduled more than 7 days apart. The oral food challenge is to be performed under double-blind conditions so that neither the subject, nor the subject's caregiver, nor any of the clinic staff (except the unblinded preparer of the challenge foods) knows which challenge contains the peanut or the placebo. The same vehicle food should be used for both parts of the DBPCFC. The clinic staff may not be unblinded as to the order of the 2 parts (peanut and placebo) of the DBPCFC until after completion of the observation period of the second part of the challenge.

The DBPCFC will consist of administering gradually increasing challenge doses of a peanut flour mixture (containing approximately 50% peanut protein) or a placebo (oat) flour mixture, mixed in a vehicle food, at 20 to 30 minute intervals. The placebo flour mixture will be supplied pre-mixed with a small amount of artificial peanut flavor to provide a reasonable

degree of taste-matching of the final placebo/vehicle food mixture to the peanut/vehicle food mixture. Additional, non-allergenic, powdered flavoring agents have been added both to the peanut and placebo flour mixtures to help further mask the distinctive flavor of peanut. A small amount of oat flour has been added to the peanut flour mixture to help match its consistency to the placebo flour mixture. Investigational sites will be provided with standardized recipes for preparation of the DBPCFC in a separate manual of procedures.

Prior to performing DBPCFC, the subject must be:

- Clear of antihistamines and other medications that could interfere with the assessment of the DBPCFC, for an appropriate length of time (5 half-lives of the antihistamine or other medications in question).
- Assessed for an exacerbation of asthma (if asthmatic) as determined by active wheezing or a PEFR < 80% of predicted.
- Free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to DBPCFC.
- Fully recovered (ie, back to their baseline state of health) from any preceding illness for at least 3 to 7 days, depending on the investigator-determined severity of the illness. Subjects should be maintained on their current, or a reduced, dose level of IP until their flare of asthma, atopic disease, or intercurrent illness has resolved.

Oral food challenges will be undertaken under direct medical supervision and with emergency medications and trained staff immediately available. The DBPCFC is performed by feeding gradually increasing amounts of a suspect allergenic food (in this case, peanut, presented as defatted peanut flour) mixed in a vehicle (matrix) food under physician observation (Bock and Atkins, 1990; Burks et al, 2012). For this study, a uniform approach to food challenge in accordance with the PRACTALL consensus guidelines for DBPCFC will be used by all investigational sites. According to the PRACTALL guidelines, the challenge doses start at 1 mg and increase in semi-log increments to a maximum dose of 3000 mg. The DBPCFC dose escalation schedules used in the current study have been modified slightly from the PRACTALL recommendations, and are presented in Table 3.

Table 3 Modified PRACTALL DBPCFC Doses Using Peanut Flour with 50% Peanut Protein Content for Screening and Exit DBPCFC

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

[a] For explanation of contingent/optional doses indicated in parentheses refer to Section 6.6.2.

For each subject, a Blinded Evaluating Physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Assessor, who is assessing and managing subject AEs on the food challenge days, is not to be involved directly in the oversight of study product dosing or the assessment or management of AEs during the initial escalation, up-dosing, or maintenance phases of the study; nor should they be involved in the preparation of the food challenge material preparation on the food challenge days (for details refer to the Masking Plan). To the extent practicable, the same Blinded Assessor who determines DLS in the Screening DBPCFC should determine DLS in the Exit DBPCFC.

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

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

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

For clarity, a tolerated dose in the context of the DBPCFCs, is defined as a dose that is successfully consumed with no more than mild symptoms, not requiring any pharmacological treatment, which are consistent with the following criteria:

- Isolated to a single organ system
- 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.

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

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

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

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

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

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

The initial (Screening) DBPCFC for eligibility will consist of administering gradually increasing challenge doses of a peanut flour mixture (containing approximately 50% peanut protein) or a placebo (oat) flour mixture, mixed in a vehicle food, at 20 to 30 minute intervals. The placebo flour mixture will be supplied pre-mixed with a small amount of artificial peanut flavor to provide a reasonable degree of taste-matching of the final placebo/vehicle food mixture to the peanut/vehicle food mixture. Additional, non-allergenic,

powdered flavoring agents have been added both to the peanut and placebo flour mixtures to help further mask the distinctive flavor of peanut. A small amount of oat flour has been added to the peanut flour mixture to help match its consistency to the placebo flour mixture. Investigational sites will be provided with standardized recipes for preparation of the DBPCFC in a separate manual of procedures.

The Screening DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in a fixed sequence without repeating any dose. The procedure will also be modified in that the highest dose will be capped at 300 mg (444 mg cumulative) peanut protein or placebo, as shown in Table 3. Otherwise, the PRACTALL recommendations for maintaining safety and assessing symptom severity serve as useful guidelines.

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

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

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

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

Dosing with food challenge materials should continue on the days between the 2 parts of the Exit DBPCFC, according to the same dosing guidelines that apply throughout the Maintenance Period.

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

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

6.7 Assessment and Treatment of Allergic Reactions to Peanut OIT

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

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

Mild symptoms:

- Skin – limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema), or pruritus (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 3)

6.7.2 Assessment of the Tolerability of an Individual Dose of IP

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

In general, the severity of allergic symptoms elicited at a particular dose of IP will define the tolerability of that dose of IP. The place where there is the greatest need for clinical judgment in determining the tolerability of a dose is when the dose elicits mild allergic symptoms. Table 4 illustrates the likely combinations of symptom severity and tolerability.

Table 4 Allergy Symptom Severity and IP Dose Tolerability

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

[a] Mild, persistent gastrointestinal symptoms lasting several days may be not tolerated (Section 6.7.3.1).

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

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

Mild symptoms: When dosing with IP 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 on the basis of 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. If, however, an allergic response to dosing is characterized by mild symptoms that do not meet all of the above criteria (eg, has mild symptoms occurring in 2 or more organ systems, requires treatment with 2 doses of antihistamine or 1 dose epinephrine, shows progression in severity or distribution over time, is protracted in duration, or includes objective wheezing), then even though the allergic symptoms may be mild, the dose should be assessed as not tolerated. If a dose elicits mild symptoms that do not fit all of the above criteria and the dose is assessed to

be tolerated, then a brief explanation as to why the dose was considered tolerated must be recorded in the CRF.

Moderate symptoms: In general, if a dose elicits moderate symptoms, the dose will be assessed as not tolerated. 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 CRF as to why the dose was considered tolerated.

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

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

6.7.3 Assessment of the Tolerability of a Dose Level

6.7.3.1 Assessment of Acute Symptoms Occurring After Dosing

With the report of moderate or severe symptoms occurring during home-dosing, the dose level should be considered to be not tolerated and the subject brought to the clinic the day after the emergence of the symptoms for administration of the next dose under medical supervision. If a dose administered at home is suspected to have been not tolerated, even on the basis of mild symptoms, the subject should also return to the CRC for dosing under medical supervision.

The recurrence of a mild symptom(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 in Section 6.7.2.

- If the site is notified of mild dose-related symptoms on 4 or more occasions during a 7-day period, the subject should return to the CRC for dosing under direct observation for assessment of the tolerability of the dose level.
- If mild dose-related symptoms are noted on 7 or more occasions during a 2-week dosing interval at a given dose level, that dose level should be considered not tolerated and appropriate action should be taken (Section 6.7.5.2).

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

6.7.3.2 Assessment of Chronic/Recurrent Symptoms

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

If symptoms arise that suggest a chronic/recurrent reaction to IP, the dose level should be reduced. As with acute symptoms, the level of the dose reduction should be guided by the severity of the symptoms. Symptomatic treatment is permitted (Section 5.9), but should be used as a supplement to dose reduction, not a substitute for it.

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

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

For subjects who develop dose-limiting chronic/recurrent GI symptoms at the 40 mg/d dose level or above, dose reduction and re-escalation is to proceed as described in Section 6.3.3.

6.7.4 Treatment of Acute Reactions to Peanut OIT During Initial Escalation

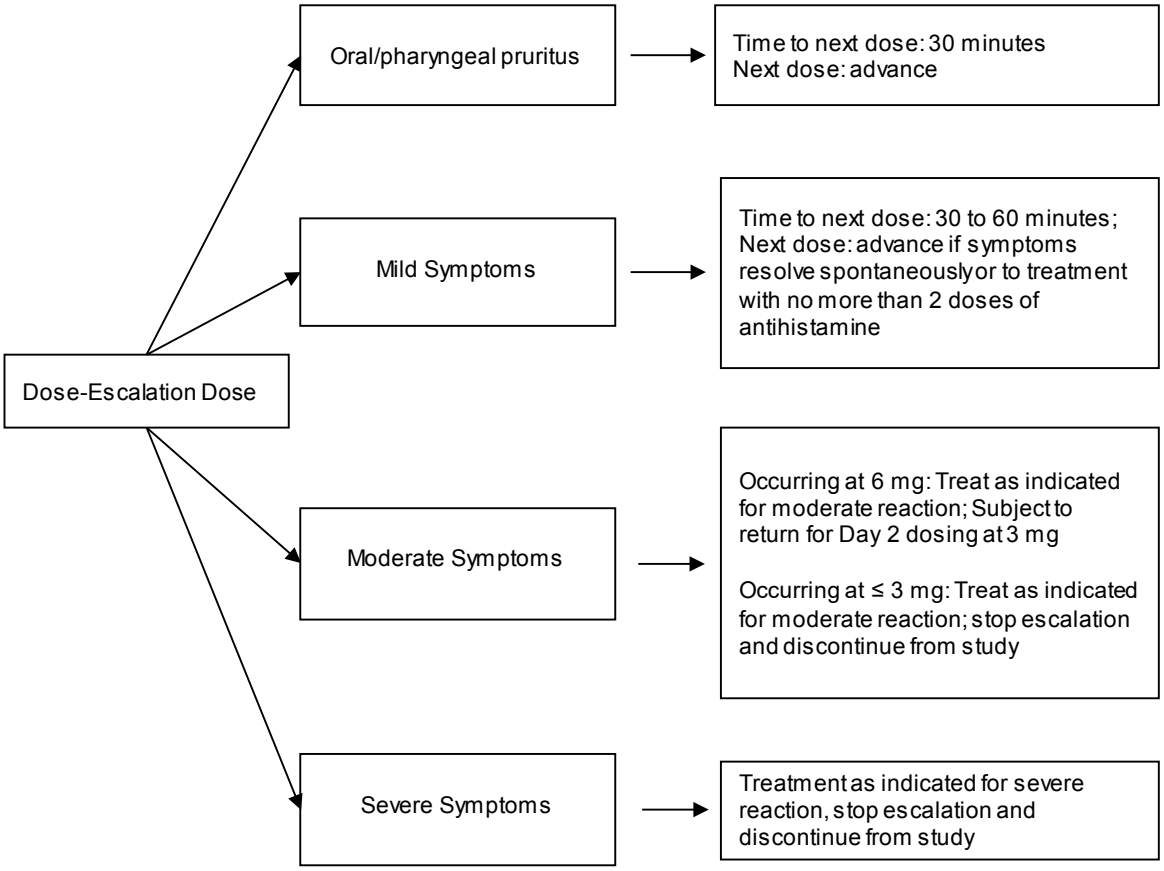
The process algorithm for responding to acute allergic symptoms during OIT is shown in Figure 2. Explanatory text follows the figure.

Investigator judgment will be required to determine the best course of action. An Aimmune medical monitor will be available at all times to answer any questions or to assist in any decisions related to the study protocol. Possible actions are listed below:

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

- Treating additionally with epinephrine, beta-agonist, oxygen, IV fluids, and/or glucocorticosteroids, as necessary, and discontinuing dose-escalation
- Discontinuation of desensitization protocol

Figure 2 Schematic for Management of Symptoms Occurring During Initial Escalation Day 1



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

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

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

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

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

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

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

The medical monitor will answer any questions and assist in any decisions related to the study protocol.

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

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

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

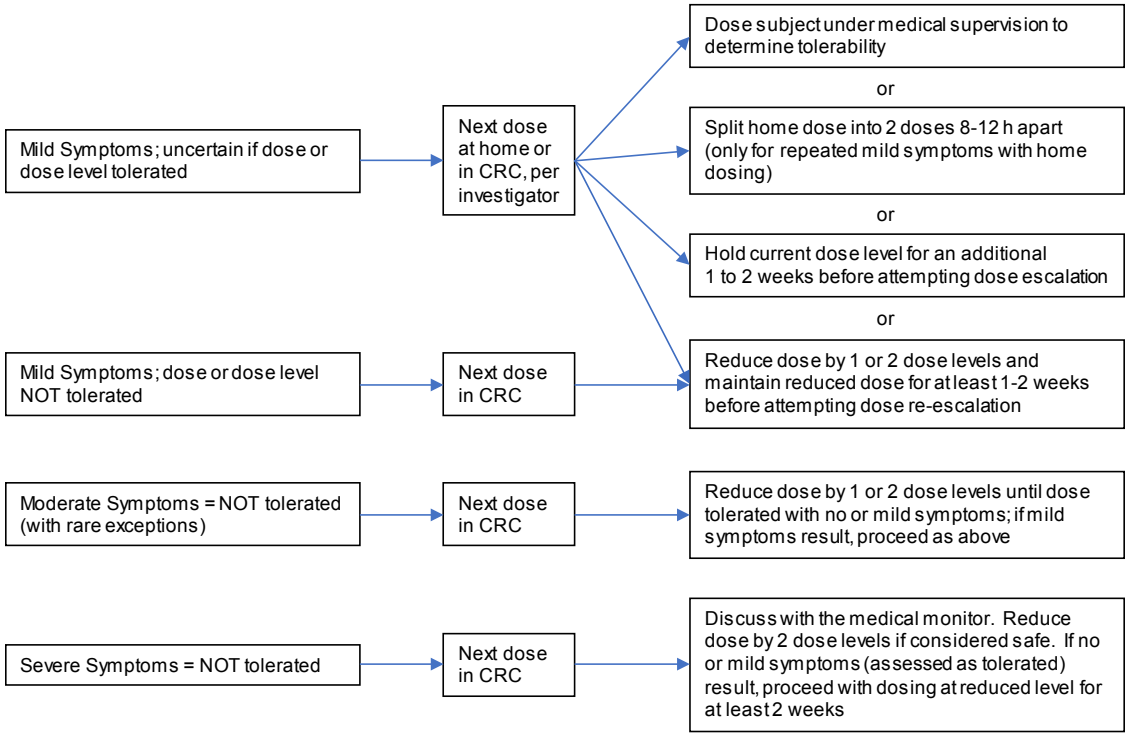
- Reducing dose by 1 or 2 dose levels and maintaining the reduced dose level for at least 1 to 2 weeks before attempting dose re-escalation – Generally, this should be the action taken when a dose that has been observed in the CRC is assessed as not tolerated, if a dose elicits moderately severe symptoms, or if the investigator is convinced of the intolerability of the current dose level. In short, it should be considered the default action whenever a dose or dose level is assessed as *not tolerated*.
- Reducing dose level for less than the usual 2-week period – this may be instituted as treatment for an intercurrent AE, to aid the investigator in determining if a dose level is or is not tolerated, or if a pattern of decreased IP tolerability during menses is discerned. The level of the reduction in dose, ranging from a 1-step reduction to a 50% reduction will be at the investigator's discretion, based on clinical judgment. The manner in which dose escalation may resume will depend on the level and the duration of the dose reduction.
- Temporarily withholding IP dosing – this may be instituted as treatment for an intercurrent AE or to aid the investigator in determining if a dose level is or is not tolerated, but the duration of withholding IP may not exceed 14 consecutive days, or the subject will be discontinued from the study. The manner in which dosing may resume after withholding dosing of IP depends on the duration for which dosing was withheld.
- Reducing dose by 1 or 2 dose levels and maintaining the reduced dose level for a duration of time recommended by the investigator – this is instituted if epinephrine is given to treat a dose-related allergic reaction. The dose reduction is per investigator discretion based on the type and severity of symptoms (Section 6.7.6).
- Stopping dosing and discontinuing the subject early from the study – this is an option that the subject may elect at any time and for any reason. The investigator must discontinue the subject from further dosing and continuation in the trial under circumstances that could jeopardize the health of the subject or the integrity of the trial.

6.7.5.1 Reactions During the Up-dosing Period

If symptoms arise in the clinic after up-dosing, the investigator is to determine whether or not the dose was tolerated (Section 6.7.3). The process algorithm for continued dosing after dose-related symptoms occur is depicted in Figure 3. Explanatory text follows the figure.

Dose adjustment after administration of antihistamines and/or epinephrine for dose-related allergy symptoms is described in Section 6.7.6.

Figure 3: Schematic for Up-dosing Period Dose Adjustment



- **No symptoms:** If a subject has a dose escalation in the CRC without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the CRC for the next scheduled dose escalation visit 2 weeks later.
- **Oral/pharyngeal pruritus:** If a subject experiences *oral/pharyngeal pruritus* following the administration of the first dose at a new dose level, the dose will generally be *assessed as tolerated*, and the same dose can be repeated the next day at home and continued throughout the 2-week home-dosing interval, unless other symptoms begin to develop.
- **Oral/pharyngeal pruritus:** If only *oral/pharyngeal pruritus* occurs following the administration of the first dose at a new dose level, the dose will generally be *assessed as tolerated*, and the same dose can be repeated the next day at home and continued throughout the 2-week home-dosing interval, unless other symptoms begin to develop.

- **Mild symptoms assessed as tolerated:** If *mild symptoms* occur with the first dose at a new dose level and the dose is *assessed as tolerated*, the action taken should be to repeat the same dose the next day. It is advised that the repeat (next day's) dose be administered in the CRC, but it may be given at home, at the investigating physician's discretion. If the second dose at the new (increased) dose level is tolerated without symptoms, then the subject is to continue on that dose level for the requisite 2 weeks and return to the CRC for up-dosing at the next scheduled visit. If the dose again causes mild symptoms, but is *assessed as tolerated*, the subject may continue at that dose level or return to the last tolerated dose (at the investigator's discretion) and continue dosing at home for the next 2 weeks at the investigator-determined dose level. (Section 6.7.5.2 for actions to be taken in the event that symptoms develop during home-dosing.) If, following the first dose at a new dose level, the second dose at the new (increased) dose level is again accompanied by mild symptoms, but is *assessed as not tolerated*, the procedures outlined in the paragraph above should be followed.
- **Mild symptoms indicating uncertainty regarding tolerability:** If other mild symptoms occur that indicate uncertainty regarding tolerability, the investigator will determine whether the subject should receive the next dose in the CRC or at home. If the investigator determines that the subject requires medical supervision to determine tolerability, the subject will receive the next dose at the CRC. If the investigator determines that the subject does not need medical supervision, the procedure will be to split the home dose into 2 doses taken 8 to 12 hours apart OR hold the current dose level for an addition 1 to 2 weeks OR reduce the dose by 1 or 2 dose levels and maintain the reduced dose for at least 1 to 2 weeks before attempting dose re-escalation.
- **Mild symptoms assessed as not tolerated:** If other *mild symptoms* occur with the first dose at a new dose level and the dose is *assessed as not tolerated*, the action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose (ie, a 1-step dose reduction) under medical supervision (if the subject is unable to return to the CRC on the day specified, the investigator may initiate an approximate 1 dose-level reduction at home, with the subject coming to the CRC at the earliest date possible). If the reduced dose is *assessed as tolerated*, the subject is to continue on that daily home dose for at least 1 to 2 weeks. (Section 6.7.5.2 for actions to be taken in the event that symptoms develop during home-dosing.) If the reduced dose is again *assessed as not tolerated*, the subject is to return to the CRC the next day for supervised dosing at a 1- or 2-step reduction in dose (per investigator judgment, based on severity of reaction). If this further reduced dose is *assessed as tolerated*, the subject will continue at that dose level for daily home-dosing over the ensuing 2 weeks. If, however, the reduced dose is *assessed as not tolerated*, the subject is to be considered an escalation failure non-responder.
- **Moderate symptoms:** If *moderate symptoms* occur with the first dose at a new dose level, except for rare instances, the dose will be *assessed as not tolerated*. The action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose under medical supervision. If this reduced dose elicits no allergic symptoms (ie, is well tolerated), the subject will continue on that daily home dose

level for an additional 2 weeks. If the subject experiences mild symptoms at the reduced dose, the procedures for responding to a dose with mild symptoms should be followed (above and Figure 3). If the subject experiences moderate symptoms at the reduced dose level, the subject should return to the CRC the next day and receive a further 1- or 2-step dose reduction (per investigator judgment). If this reduced dose is well tolerated, it will be continued as the daily home dose for at least 2 weeks before re-escalation is attempted in the CRC. If the dose is not well tolerated, but elicits mild symptoms, then the treatment procedures for responding to mild symptoms should be followed (above and Figure 3). If, however, the subject again experiences moderate symptoms at the reduced dose level, a discussion with the medical monitor is to ensue to reach a decision as to whether to continue the subject in the study.

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

- **Severe symptoms:** If *severe symptoms* occur, the action should be to treat the subject for the allergic reaction, and then, in consultation with the medical monitor, decide whether or not to discontinue the subject from the study. If it is determined that it is safe to allow the subject to continue in the study, the subject should return to the CRC the next day for dosing at a 2-step reduction in dose under observation. If the subject tolerates the dose reduction (ie, shows no or only mild symptoms that are assessed as tolerated), then the subject is to remain at the reduced dose level for at least 2 weeks before returning to the CRC to attempt dose re-escalation. If the subject does not tolerate the reduced dose, then the subject is to be considered an escalation failure non-responder.

Consult the medical monitor for specific questions related to dose escalation or continuation of the same dose that are not answered in the procedures described above.

6.7.5.2 Reactions to Dosing at Home

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

When symptoms of a dose-related allergic reaction are reported during the course of daily home-dosing, the investigator must assess the severity of the reaction and whether the dose associated with the reaction was tolerated. The appropriate intervention will depend on the type and severity of symptoms (Figure 3).

In general, moderate or severe symptoms will be considered clinically significant, and any dose eliciting such symptoms *assessed as <u>not</u> tolerated*; however, mild symptoms may also be considered clinically significant (eg, if affecting multiple organ systems, increasing in

intensity, occurring with increasing frequency, or affecting a larger area over time) and *assessed as not tolerated*. Whenever there is question as to the clinical significance of mild signs or symptoms, the investigator should have the subject return to the CRC for observed dosing under medical supervision.

For home-doses *assessed as not tolerated* on the basis of acute dose-related symptoms, the same procedures described in Section 6.3.3 for adjusting up-dosing should be followed. Dose adjustment after administration of antihistamines or epinephrine for dose-related allergy symptoms is described in Section 6.7.6.

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

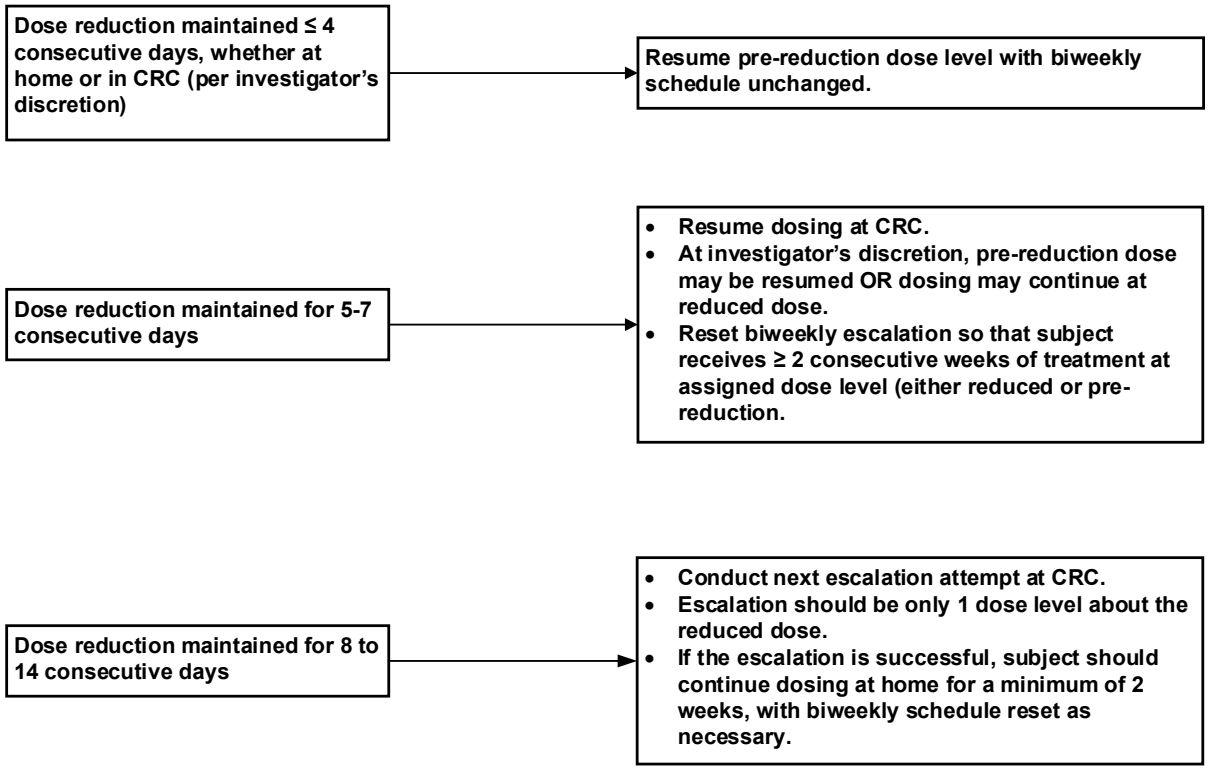
- Continue with daily home dosing at the current dose level
- Continue the same daily dose for the rest of the 2-week interval, with the dose split into 2 fractional doses given 8 to 12 hours apart (the 2 fractional doses need not be equal)
- Return to the CRC for repeat dosing at the current dose level under direct observation to confirm whether or not the dose level is tolerated
- Return to the CRC for dosing of a previously tolerated dose level, either a 1- or 2-step reduction (per investigator judgment, based on severity of reaction) and follow the procedures described in Section 6.7.5.2.
- Institute the 4-week hiatus from dosing, with resumption of dosing at the 3 mg/d dose level, as permitted for recurrent GI symptoms occurring at or before the 20 mg dose level, as described in Section 6.7.3.2.
- Discontinuation of dosing

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

6.7.5.3 Temporary Dose Adjustment in Response to Intercurrent Adverse Events

At the investigator'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 IP during menses is discerned, then a temporary dose reduction can be instituted during this time. The procedures for temporary dose reduction due to intercurrent AEs are provided in Figure 4. Explanatory text follows the figure.

Figure 4: Schematic for Temporary Dose Reductions due to Intercurrent Adverse Events



Temporary dose reductions for intercurrent AEs may be instituted as follows:

- For dose reductions of **≤ 4 consecutive days**, whether dose re-escalation is to occur at home or in the CRC is at the investigator's discretion. If the reduction in dose is maintained for ≤ 4 consecutive days, then the pre-reduction dose level (ie, the dose level last tolerated) 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 at least 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 of IP may also be withheld at the investigator's discretion, in response to an intercurrent AE. Doses withheld as part of the treatment for an AE constitute a special category of missed peanut OIT doses (Section 6.8).

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

The treatments for reactions during the Up-dosing Period are summarized by severity of reaction in Table 5.

Table 5: Treatment(s) for Reactions during the Up-dosing Period by Severity of Reaction

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

Assessment of severity of reaction is described in Section 6.7.1. Assessment of tolerability of an individual dose is described in Section 6.7.2.

- **General Approach:** Treatment of acute reactions should be with either an antihistamine and/or epinephrine, along with IV fluids, a beta-agonist (eg, albuterol, by inhaler or nebulizer), oxygen, and/or corticosteroids, as indicated.
- Many **mild** acute allergic reactions can be transient and self-limiting, requiring no therapeutic intervention. Others, however, may require treatment. Generally, for mild symptoms requiring treatment, the subject should receive antihistamines.
- Acute allergic reactions manifesting with **moderate** symptoms will generally require therapeutic intervention, although some, even moderate, symptoms may on rare occasion be so transient as to require no specific treatment. Generally, for moderate symptoms requiring treatment, the subjects should receive antihistamines and/or epinephrine, as indicated. If there is uncertainty as to the severity of the reaction, administering epinephrine would be considered the most appropriate course of action.
- Generally, **severe** symptoms will require treatment with epinephrine at a minimum.

The procedures(s) that should be implemented after treatment of a reaction experienced during the Up-dosing Period are summarized in Table 6. An explanation follows the table.

Table 6: Procedure(s) Following Treatment of a Reaction Experienced during the Up-dosing Period

Treatment Given for a Reaction	Procedure(s) Following Treatment
Antihistamines only	Continue dose escalation
Epinephrine: 3 or more doses given for dose-related allergy symptoms or anaphylaxis	• Stop study product dosing • Subject is to return to the CRC 14 days after the last dose of study product for the Early Discontinuation Visit (Section 6.4)
Epinephrine given in CRC	• 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 (Section 6.7.5, Figure 3), and administer in the CRC • 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 CRC • 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 (Section 6.7.5, Figure 3), and administer in the CRC under medical supervision prior to resuming any dosing at home • Following severe allergy symptoms, discussion with the medical monitor is strongly recommended

CRC=clinical research center.

- Antihistamines

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

- Epinephrine – General

  Any reaction to IP (in clinic or at home) that requires 3 or more doses of epinephrine will halt all further dosing of IP for the individual. The subject will be asked to return to the CRC 14 to 16 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.4).

- Epinephrine – Clinic

  If administration of epinephrine is required during, or after, a dose-escalation in the clinic, or for anaphylaxis, no further dosing of IP is to occur at that visit. The next

dose of IP is to be reduced by 1 or 2 dose levels per investigator discretion based on the type and severity of allergy symptoms (Section 6.7.5, Figure 3), 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.

If administration of epinephrine is required a third consecutive time, no further dosing should be attempted. Dosing in these subjects will be discontinued. They will be asked to return to the CRC 14 to 16 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.4).

- Epinephrine – Home

  Administration of epinephrine outside of the clinic should be followed immediately by the subject being taken to the nearest ER. 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.

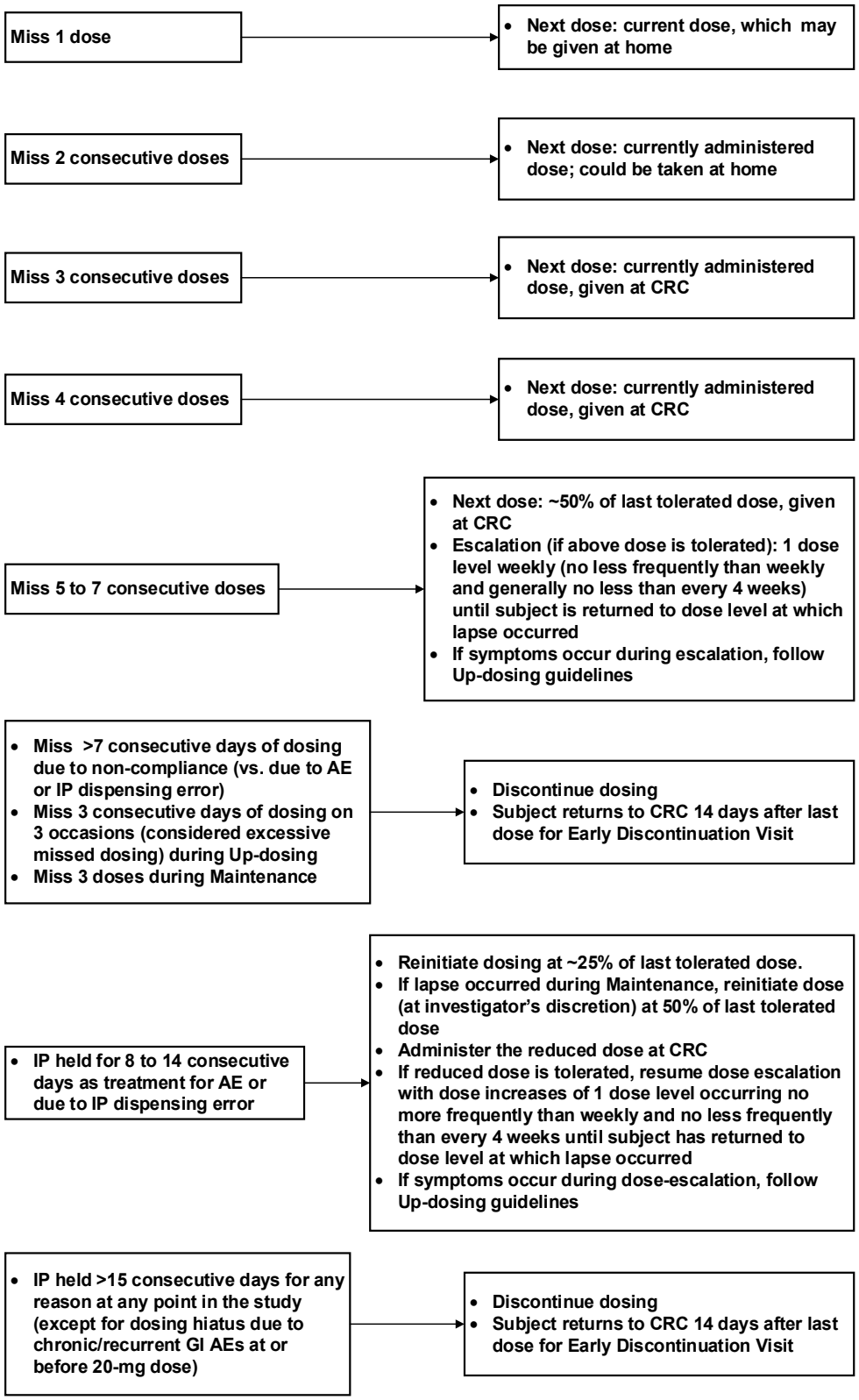
6.7.7 Reactions Occurring During the Maintenance Period

This phase consists of the subject receiving the 300 mg/d dose of IP for approximately 12 weeks. For any noted symptoms during the Maintenance Period, the same IP dosing guidelines and procedures will be followed as for the Up-dosing Period.

6.8 Missed Peanut OIT (IP) Doses During Up-dosing

Risk due to missed doses of study product is believed to be highest during the Up-dosing Period. The procedures to be followed after missed consecutive doses of study product during the Up-dosing Period is depicted in Figure 5. Explanatory text follows the figure.

Figure 5: Procedures Following Missed Consecutive Doses of Peanut OIT



AE= AE; GI=gastrointestinal; CRC=clinical research unit; IP=investigational product

- Miss **1 dose** – The next dose would be at the current dose level and could be given at home.
- Miss **2 consecutive doses** – The next dose would be the current dose level and could be given at home.
- Miss **3 consecutive doses** – The next dose would be the current dose and would be given under supervision in the CRC.
- Miss **4 consecutive doses** – The next dose would be the current dose and would be given under supervision in the CRC.
- Miss **5 to 7 consecutive doses** – Initiate the next dose at approximately 50% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 50% of the last tolerated dose). This dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1 dose level occurring no more frequently than weekly and generally no less frequently than every 4 weeks until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the Up-dosing Period apply.
- Missing **> 7 consecutive days** of dosing due to non-compliance (ie, for any reason other than treatment of an AE or an IP dispensing error), constitutes an individual stopping rule and the subject is to stop taking IP. The subject will be asked to return to the CRC 14 to 16 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.4).
- Additionally, excessive missed dosing, defined as **3 consecutive days of missed doses on 3 occasions during the Up-dosing Period or on 3 occasions during the Maintenance Period**, for any reason other than treatment of an AE or an IP dispensing error, constitutes an individual stopping rule and the subject is to stop taking IP. The subject will be asked to return to the CRC 14 to 16 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.4).
- If IP has been withheld for **8 to 14 consecutive days** as treatment for an AE or due to a IP dispensing error, dosing may be reinitiated at approximately 25% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 25% of the last tolerated dose) if the lapse in dosing occurred during the Up-dosing Period. If the lapse in dosing occurred during the Maintenance Period, dosing may, at the investigator's discretion, be reinitiated at 50% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 50% of the last tolerated dose). The reduced dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1 dose level occurring no more frequently than weekly and no less frequently than every 4 weeks until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the Up-dosing Period apply.
- If IP has been withheld for **≥15 consecutive days** for any reason, at any point in the study (with the exception of a dosing hiatus instituted for chronic/recurrent GI AEs at or before the 20 mg dose level, as per Section 6.7.3.2), the subject will be asked to return to the CRC 14 to 16 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.4).

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

6.9 Skin Prick Test

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

6.10 Assessment of Asthma Control Using the Asthma Control Test Questionnaire

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

6.11 Visit Intervals and Windows

Screening

The Screening Period assessments should be completed within 28 days (Day -27 to Day 0).

Initial Escalation

The Initial Escalation Day 1 visit occurs within 10 days of the second day of the Screening DBPCFC and must occur within 6 weeks of signing of the consent/assent form (preferably by 28 days). The exceptions to this are if a subject experiences an AE as a result of the DBPCFC, or due to scheduling difficulties, in which case an extension to the Screening window should be agreed with the medical monitor.

Up-dosing Period

For all Up-dosing Visits, which occur every 2 weeks, there is a ± 3-day visit window. Regardless of visit intervals subjects must continue with daily dosing of IP.

Maintenance Period

The Maintenance Period lasts for approximately 12 weeks but may be extended up to a maximum of 16 weeks or to a maximum of study duration of 56 weeks, whichever is shorter (Section 6.3.3.3). There is a ± 3-day visit window for all visits in the Maintenance Period.

The first Maintenance Visit is 2 weeks after the 300 mg Up-dosing Visit. The next 3 visits are at 6, 10, and 12 weeks after the 300 mg Up-dosing Visit. If at 12 weeks after the 300 mg Up-dosing Visit the subject has maintained a dose of 300 mg/d for approximately 12 weeks, without the use of symptomatic therapy for at least the last 4 weeks, the Exit Visit will be performed. If that is not the case, then the subject will continue in the study for up to 4 more weeks of 300 mg dosing before proceeding to the Exit Visit.

Exit Visit

The Exit Visit will occur after 12 to 16 weeks after a subject commenced dosing at 300 mg/d.

Early Discontinuation Visit

An Early Discontinuation Visit should occur 14 to 16 days from the last dose of IP.

Unscheduled Visits

Unscheduled Visits may occur at any time during the study.

6.12 Study Blinding Procedures

This is a double-blind study. The study as a whole will not be unblinded until after the last subject exits ARC010 and the database is locked.

After undergoing the Exit DBPCFC, most subjects will, however, become de facto unblinded to their on-study treatment assignment on the basis of their experience with the food challenge (ie, subjects who fail 1 part of the Exit DBPCFC early on may reasonably deduce that they had been in the placebo arm of the study), and those who tolerate both parts of the Exit DBPCFC (or fail 1 part only at the highest dose levels tested) may reasonably deduce that they had been in the AR101 arm. Hence, the study is double-blinded on an individual subject basis only up to completion of the Exit DBPCFC. It is for this reason that assessment of reactions to DBPCFC will be made by a Blinded Evaluating Physician (Blinded Assessor).

The risk of bias being introduced into the determination of DLS during DBPCFCs will be substantially reduced by having the assessment of the DBPCFC results made by a Blinded Evaluating Physician (Blinded Assessor) who is not otherwise directly involved, during the treatment phase, with the treatment of the subjects he or she is evaluating.

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

Subjects who discontinue the study prior to the Exit DBPCFC are not unblinded until after database lock and unblinding of the study as a whole.

6.12.1 Securing Blinding and Randomization Information

Aimmune or one or more of its contractors will manufacture, package, label, store, and distribute the IP. During site visits, the site monitor will check the clinic and/or pharmacy

logs to ensure that appropriate randomization assignments are received, recorded, and maintained.

6.12.2 Requirements for Unblinding

Prior to the Exit DBPCFC assessment, a subject may be unblinded only when needed for making medical decisions regarding the care of a subject. In the event of such a medical emergency, the investigator is able to make the decision to unblind a subject, but is requested, where possible, to discuss this with the sponsor's medical monitor. If a life-threatening event occurs, the subject should be treated as if the subject received active IP. For all non-life-threatening events that require unblinding (eg, AE which may result in persistent or significant disability/incapacity), the investigator may contact the clinical monitor who will coordinate with the sponsor's representatives.

6.12.3 Breaking the Blind

Site personnel or other study team members (such as the medical monitor) may request emergency unblinding as described in Section 6.12.2.

In case emergency unblinding is necessary, the interactive response system allows study personnel with appropriate permissions to request unblinding for a specific subject. An automated notification is then sent to the sponsor and the sponsor's safety designees to inform them of the unblinding. A built-in audit trail documents the unblinding process and the persons involved. In the event that the interactive response system is not available, a phone number is provided to all sites in the interactive response system manual for use in the situation of emergency unblinding. Unblinding is possible 24 hours a day, 7 days a week.

6.12.4 Documenting and Unblinding

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

7. SAFETY MONITORING

This section defines the types of AEs that should be reported and outlines the procedures for appropriately collecting, grading, recording, and reporting them. A DSMC will be established to monitor study safety events and will meet at time points defined in the DSMC charter.

7.1 Definitions for Recording of Safety Events

All safety events observed under this protocol are captured throughout the duration of the study. Some safety events arising under certain defined conditions are recorded on specific forms as follows.

- Any allergic symptoms observed during in-clinic dosing will be recorded directly on the Escalation/In-Clinic Dosing form (also referred to as an IP Administration form), and are not recorded on an AE form in the CRF (to avoid duplicate reporting) unless the event is considered an SAE. These symptoms are, however, by definition, AEs (Section 7.2) and will be reported as such in the database.
- Safety events related to accidental food exposure are recorded on an Allergic AE form. They are not to be reported on an AE form (to avoid duplicate reporting) unless the event is considered an SAE, as defined below (Section 7.3.2).
- For any event occurring after the informed consent/assent form has been signed that meets the definition of anaphylaxis (Appendix 3), an Allergic AE form will be completed and forwarded to the drug safety vendor within 24 hours of its occurrence and/or the site's being notified of the event (Section 7.3.3.1).
- If any safety event meets the definition of an SAE (whether or not related to dosing), it will also be recorded on an SAE paper/pdf form (in addition to the CRF form). With the exception of an anaphylaxis event that is also an SAE, the Anaphylaxis form should be completed and the 'SAE' box on this form checked.
- SPT reactions are not considered AEs unless the reaction, or a complication from the procedure, is considered an SAE, as defined below (Section 7.3.1.1).
- Food challenge reactions that occur in the clinic are captured on study specific forms and are not reported on an AE form (to avoid duplicate reporting) unless the event is considered an SAE, as defined in Section 7.3.1.1.
    - As IP is not used in the DBPCFCs, no AEs occurring from Screening DBPCFC can be treatment-related (referring to treatment with IP).
    - For food challenge reactions that occur at the Exit DBPCFC, it will also usually be the case that IP was not the cause of the reaction, as IP is not used in the challenge. There is, however the possibility that dosing with IP in the days prior to Exit DBPCFC could contribute to a reaction encountered during the challenge. The investigator must determine if dosing with IP in the days prior to Exit DBPCFC likely contributed to any observed reaction. If so, the investigator should indicate the level of the relatedness, and provide a brief explanation as to the manner in which prior dosing with IP was thought to be contributory.
- All SAEs are reported on the AE/SAE form (in the CRF) set in addition to the Skin Prick Test form or an Oral Food Challenge form if the event occurred during 1 of these procedures. All other safety events that occur throughout the study are reported on the AE/SAE form set.

7.2 Dosing Symptoms as Adverse Events

Although signs and symptoms of allergic reaction, especially those that are mild in severity, are frequent and expected occurrences in response to dose escalation during OIT, they still constitute AEs. As such, the start and stop times of dose-related allergic reactions, as well as any therapeutic interventions, and relatedness to IP will need to be recorded (Section 7.8.1).

It is common for allergic reactions, especially allergic reactions to food allergens, to manifest with multiple symptoms. When multiple symptoms are noted during the same episode, it is up to the investigator to determine whether one, or more than one, AE has occurred. For allergic/ hypersensitivity reactions involving multiple symptoms, each individual symptom is to be entered on a separate log line on the CRF. For each symptom, the AE CRF will query 'Is this an allergic reaction?' and the site should indicate yes or no accordingly.

7.3 Definitions

7.3.1 Adverse Event (AE) or Medical Event

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

An **adverse reaction** is any AE caused by the IP.

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

7.3.1.1 Suspected 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.

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

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

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

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

7.3.3 AEs of Interest

7.3.3.1 Anaphylaxis

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

With respect to the inclusion of being "potentially life-threatening" in the definition of anaphylaxis and how that relates to the assessment of anaphylaxis as an SAE, reference is made to the 2012 Food and Drug Administration (FDA) Guidance for Industry and Investigators, "Safety Reporting Requirements for INDs and BA/BE Studies," (BA/BE = bioavailability/ bioequivalence) that states, "An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death." Thus, for the reporting of anaphylaxis as an SAE, the severity of the reaction, assessed according to the EAACI system for grading the severity of anaphylactic reactions (Muraro et al, 2007), is also to be taken into account (Section 7.6 and Appendix 3).

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

7.3.3.2 Gastrointestinal AEs Resulting in Prolonged Disruption of Dosing (Events of Interest)

Gastrointestinal AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered AEs of interest (AEIs) and will be assessed longitudinally according to the procedures described below. For the purpose of delineating these AEIs, prolonged disruption of dosing is defined as withholding IP for > 7 days. This will include 3 categories of subjects:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 6.7)

- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.7.3.2);
- Any subject who permanently discontinues dosing due to GI AEs (Section 4.3.1).

Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire, with the assistance of a parent or guardian, as appropriate, while symptomatic, at the time of treatment discontinuation, and then every month for 6 months thereafter. During the 6-month safety follow-up, subjects may complete the PEESS v2.0 at home and send it to the clinic, or they may complete it at the clinic if monthly clinic visits are required.

It should be noted that the PEESS v2.0 was not designed to establish a diagnosis of EoE, and has not been validated for use in subjects with GI symptoms of other etiologies. Furthermore, the discriminant validity of the questionnaire has not been reported in either longitudinal natural history or interventional studies. For these reasons, the use of the PEESS v2.0 to monitor the clinical course of GI symptoms must be considered exploratory. Nevertheless, the PEESS v2.0 has shown good content and construct validity (Franciosi et al, 2011; Martin et al, 2015) and so holds promise for being a valuable tool to follow the clinical course of EoE or an EoE-like immune-mediated GI syndrome. Thus, the PEESS v2.0, could reveal trends toward symptomatic improvement or worsening that might otherwise go undetected.

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

If a subject with chronic/recurrent GI AEs has not experienced complete resolution of symptoms within 6 weeks of discontinuation of dosing with the 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, at any time, and at his or her discretion, request consultation from an outside physician or additional testing to assist in the diagnosis or management of the AE.

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

7.3.3.3 Accidental Food Allergen Exposures

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

To report the occurrence of a safety event associated with accidental food ingestion, subjects will be instructed to contact the site study coordinator or investigator 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. These events will be reported as follows:

- The non-serious AEI form will be completed for each of these events, in addition to events where consumption of peanut without a reaction occurs, unless:
- The accidental food ingestion safety event meets the definition of an SAE, as defined in Section 7.3.1.1, in which case the SAE form will be completed.

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

7.3.3.4 Adverse Events Featuring a Severe Symptom

Any AE meeting the criteria for severe as defined in Section 7.6 will be reported as an AEI.

7.3.3.5 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 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.

7.3.4 Unexpected Adverse Event

An AE is “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, the Investigator’s Brochure, or the protocol.

7.3.5 Clinically Significant Laboratory Results

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

- The test result is associated with clinically significant 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 and/or;

- The test results are regarded as clinically significant by the investigator and/or medical monitor.

7.4 Adverse Event Monitoring and Recording

7.4.1 Monitoring Procedures

All AEs will be recorded from the time of signing of the informed consent form (ICF) through the Early Discontinuation/Exit Visit, including during dosing hiatus.

AE may be identified during subject visits or during the review of the subject diary. Each occurrence of an AE should be recorded separately (eg, daily abdominal pain).

All signs and symptoms associated with an AE should be recorded.

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

Each AE will be followed from its onset until the event is resolved or medically stable or until Early Discontinuation/Exit Visit, whichever occurs first. AEs ongoing at the time that IP is discontinued may not be determined to be medically stable until 30 days after the End of Treatment Period, in which case additional monitoring after the Early Discontinuation/Exit Visit may be required.

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

Skin prick test reactions are not considered AE unless the reaction, or a complication from the procedure, is considered an SAE, as defined in Section 7.3.1.1.

Food challenge reactions that occur in the clinic are captured on study specific forms and are not reported on an AE form (to avoid duplicate reporting) unless the event is considered an SAE, as defined below (Section 7.3.1.1).

- As study product is not used in the DBPCFCs, no AEs occurring from Screening DBPCFC can be treatment-related (referring to treatment with study product).
- For food challenge reactions that occur at the Exit DBPCFC, it will also usually be the case that study product was not the cause of the reaction, as study product is not

used in the challenge. There is, however the possibility that dosing with study product in the days prior to Exit DBPCFC could contribute to a reaction encountered during the challenge. The investigator must determine if dosing with study product in the days prior to Exit DBPCFC likely contributed to any observed reaction. If so, the investigator should indicate the level of the relatedness, and provide a brief explanation as to the manner in which prior dosing with study product was thought to be contributory.

7.4.2 Recording Procedures

All AEs will be recorded from the time of signing of the ICF through the Early Discontinuation/Exit Visit. Recording of these AEs into the eCRF is described below in the eCRF completion guidelines. In addition, SAE and AEI will be entered in a respective AE form as detailed in the AE form completion guidelines. Completion of appropriate eCRF and AE form in summarized in Table 7 below.

Any event that meets the definition of an SAE (Section 7.3.1.1) will also be reported to the drug safety vendor using an SAE report form as described in Section 7.9.1 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. Medical notes, with subject identifiers redacted, can be scanned and attached to the AE form as well.

Table 7: Adverse Event Recording

Adverse Event Type	eCRF	PV Form	Severity	Timeline	F/U
Serious Adverse Event	AE	SAE Form		< 24 hours	Y
AEI: Anaphylaxis	Allergy AE	AEI Form*	Muraro/EAACI	< 24 hours	Y
AEI: Allergic Reactions	AE	AEI Form*	CoFAR	< 24 hours	Y
AEI: Gastrointestinal AE resulting in dosing disruption	AE	AEI Form*	NCI-CTAE	< 24 hours	Y
AEI: Accidental Food Allergen Exposure	Allergy AE	AEI Form*		< 24 hours	Y
AEI: AE associated with epinephrine use	Con Meds	AEI Form*		< 24 hours	Y
AEI: Severe AE	AE	AEI Form*		< 24 hours	Y
Other: Food Challenge	FC	SAE only		< 24 hours	Y
Other: Pregnancy	Appropriate visit lab form	Pregnancy Form	NCI-CTAE	< 24 hours	Y
Other: Non-serious	AE	AEI only		< 7 days	Y

* Unless the AEI fulfils the seriousness criteria, in which case an SAE form should be completed.

7.5 Data Safety Monitoring Committee

Although the safety of peanut OIT overall is well established, a DSMC will monitor the study for safety. The DSMC will meet at time points defined in the DSMC charter to review accruing safety data. The committee will consist of individuals with extensive multicentre clinical study experience drawn from the fields of clinical immunology (specifically food allergies) and biostatistics. These individuals will be entirely independent of the conduct of the study. Further details will be provided in the DSMC Charter.

7.6 Severity Grading

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

- The severity of allergic reactions will be graded according to the definitions developed by the CoFAR group (Appendix 4).
- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 3).
- 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.

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

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

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

7.7 Guidelines for Determining Causality of an Adverse Event

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

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

7.8 Adverse Event Collection Procedures

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

AEs may be discovered through any of these methods:

- Observing the subject

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

7.8.1 AE Recording Procedures

AEs are recorded within the electronic data capture (EDC) system as detailed in the CRF completion guidelines.

7.8.2 SAE Recording and Reporting Procedures

All SAEs will be reported to the sponsor from the time of signing of the ICF through the Early Discontinuation/Exit Visit (at least 14 days after the last AR101 dose). 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 CRF. All centers are obligated to report SAEs within 24 hours of their occurrence and/or the site's knowledge of the event to the sponsor. The following attributes will be assigned:

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

The site investigator will apply his or her 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 trial procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

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

1. Notify the site's investigator.
2. Complete and transmit an AE form through the EDC system. Information regarding an SAE report must be recorded in the subject's medical chart.
3. Complete and submit an SAE Form in accordance with the SAE completion guidelines.

4. 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.
5. In the event of a death, the SAE form must be completed and transmitted along with other supporting data (death certificate, medical notes, etc).

7.9 Serious Adverse Event Notification

7.9.1 Notifying the Sponsor

Study investigators will provide the drug safety vendor with data of all SAEs as defined per the protocol on an ongoing basis.

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

7.9.2 Expedited SAE Reporting to Regulatory Health Authorities

The medical monitor will review each SAE report and will determine whether the SAE must be reported to regulatory health authorities on an expedited basis. The final decision for disposition regarding expedited reporting to the regulatory health authorities rests with the medical monitor.

The sponsor will expedite the reporting to all concerned investigator(s), the EC, where required, and to the regulatory health authorities, including (when applicable) via EudraVigilance Clinical Trial Module (EVCTM) in accordance with CT-3, Article 7.4, reports of all adverse drug reactions (ADRs) that are both serious and unexpected in accordance with ICH E6 5.16.2 and 5.17.1.

Specifically, the sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening are recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the EC no later than 7 days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other suspected serious unexpected adverse reactions shall be reported to the appropriate regulatory health authorities and to appropriate EC as soon as possible and within a maximum of 15 days of first knowledge by the sponsor. 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. The sponsor will provide the DSMC and the drug safety vendor with copies of any expedited SAE reports submitted to regulatory health authorities.

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

Finally, 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.

7.9.3 Notifying the Data Safety Monitoring Committee

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

Sites are instructed to report episodes of anaphylaxis within 24 hours of their occurrence and/or the sites being notified of the event to the drug safety vendor. Information regarding these events will be sent to the DSMC if the event is associated with any of the following:

- Fatal ADR;
- 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 Adverse Event of Interest form containing the information known to the site at the time will be transmitted to the drug safety vendor. The drug safety vendor will then relay to the sponsor and DSMC the individual anaphylaxis reports as they are obtained. The site will supplement the initial Adverse Event of Interest form with additional information pertaining to an event as it becomes available and will forward the information to the drug safety vendor.

7.9.4 Notifying the Institutional Review Board and Ethics Committee

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

Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the EC with a listing of all suspected serious adverse reactions that have occurred over this period and a report of the safety of subjects.

7.10 Other Safety Assessments and Precautions

7.10.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in Appendix 1 Schedule of Events. Height and weight will also be recorded at specified visits. Vital signs will be measured, including BP, pulse rate, and body temperature. Except where a full, age appropriate, physical examination is specifically indicated, a symptom-directed physical exam may be performed.

7.10.2 Prior and Concomitant Medications

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

7.10.3 Pregnancy Testing and Contraception

7.10.3.1 Pregnancy Testing

All female subjects of childbearing potential will undergo a serum pregnancy test at Screening and then urine pregnancy test at subsequent visits.

Females of childbearing potential are defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following criteria: at least 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40 IU/L or at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy or hysterectomy, OR are using one of the methods of highly effective contraception listed in Section 7.10.3.2.

Although pregnancy itself is not considered an AE or an SAE, if a subject becomes pregnant during the course of the study the pregnancy must be reported to the sponsor and the subject should be followed to term or until termination.

7.10.3.2 Contraception

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

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

Study personnel are requested to address questions of sexual history and counselling in relation to contraception using sensitivity and a patient-centered approach and, if possible, to hold discussions regarding sexual history and contraception with adolescent female subjects in a private setting.

Female subjects are to use a highly effective single 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. Acceptable methods of birth control are the following:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Sexual abstinence

7.11 Stopping Rules

7.11.1 Overall Stopping Rules

The study will be suspended at any time if a treatment-associated death occurs in a subject on active therapy, or if the second of 2 subjects is admitted to the hospital, within 6 months of the first, as a direct consequence of dosing with IP. Suspension of the study will entail halting the enrollment of subjects and refraining from any dose increases, but will not entail cessation of dosing unless so directed by the relevant regulatory agency(ies), or advised by the DSMC and agreed to by the sponsor. The suspension will not be lifted and dose escalation will not be resumed until the information has been discussed with regulatory authorities and the regulatory authorities either concur with resumption of up-dosing or direct discontinuation of the study in their jurisdictions.

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

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

In the event of early study closure, subjects who complete at least 9 months of study treatment and tolerate the 300 mg/d dose for at least 4 weeks may have the Exit DBPCFC and complete the study. AR101-treated subjects who tolerate a single highest challenge dose of at least 300 mg peanut protein (443 mg cumulative) in the Exit DBPCFC and placebo-treated subjects will be eligible to enroll in ARC008. In this situation, AR101-treated subjects who complete at least 9 months of study treatment and tolerate 300 mg/d for at least 4 weeks, but do not tolerate the single challenge dose of 300 mg peanut protein in the ARC010 Exit DBPCFC, may enroll in ARC008 if continued treatment is determined to be safe per investigator judgment and after discussion with the medical monitor. AR101-treated subjects who complete at least 9 months of study treatment but do not tolerate 300 mg/d for at least 4 weeks will not have the Exit DBPCFC but may be eligible to enroll in ARC008 if continued treatment is determined to be safe per investigator judgment and after discussion with the medical monitor.

7.11.2 Individual Stopping Rules

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

Occurrence of any of the following will result in the cessation of dosing:

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

8. IMMUNE CELL CHARACTERIZATION

Humoral (immunoglobulin; antibody) immune assays will be performed at Screening, at the 300 mg Up-dosing Visit, and at the Exit or Early Discontinuation Visit. The blood samples for these serum-based assays can and should be collected with the same blood draw as the CBC.

8.1 Peanut-Specific Antibody (Immunoglobulin) Assays

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

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

At each of the specified time points, a sample of serum will be stored for assessment of peanut- and peanut component-specific antibody levels (immunoglobulin assays). Total IgE and specific IgE and IgG4 will be measured using UniCAP. Peanut-specific IgE and IgG4 (included in the immunoglobulin assays) will be measured at the Screening, 300 mg Up-dosing, Exit, and Early Discontinuation Visits. Additionally, as part of the Screening/Baseline immunoglobulin assays, component-resolved (peanut component proteins) peanut IgE testing will be performed. The amount of blood to be drawn will be determined on the basis of the requirements of the test and individual laboratory protocols, in compliance with local regulations.

9. STATISTICAL CONSIDERATIONS

This section outlines the major statistical consideration for Study ARC010. A comprehensive statistical analysis plan (SAP) will be finalized prior to overall study unblinding.

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

All data will be listed for all subjects.

9.1 Analysis Populations

The ITT population (ie, the Full Analysis Set) will consist of all randomized subjects who received at least 1 dose of randomized study treatment (AR101 or placebo). Subjects will be analyzed according to randomized treatment. The ITT population will be used as the primary analysis population for all analyses of efficacy endpoints.

Since only a small number of subjects are expected to be randomized but not treated and due to the double-blind nature of the trial, no bias is introduced by excluding these subjects from the ITT population. In order to verify this expectation, sensitivity analyses will be performed using the randomized population for the primary and key secondary endpoints.

The Completer population will include all subjects in the ITT population who undergo the Exit DBPCFC.

A Per Protocol (PP) population may be defined for this study. The PP population will be a subset of the Completer population, limited to subjects who have no major protocol deviations that may influence the desensitization response. Exclusions will be determined by blinded review before database lock and overall study unblinding. Subjects will be analyzed according to randomized treatment.

Sensitivity analyses, to be described in full in the SAP, will be performed using the Completer population and PP population (the latter if sufficiently different from the Completer population).

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

9.2 Study Endpoint Assessment

9.2.1 Primary Endpoint

The primary endpoint is the proportion of subjects who achieve desensitization as determined by tolerating 1000 mg as a single dose (2043 mg cumulative) of peanut protein (ie, a top single challenge dose of 1000 mg) with no more than mild symptoms at the Exit DBPCFC (ie, responders).

An ITT analysis will be performed as the primary efficacy analysis to test for a treatment difference in the response rate. All individuals failing to achieve the success definition described above will be considered treatment failures, as will subjects who fail to achieve and maintain a 300 mg daily dose of IP (escalation failure non-responders). All individuals

who drop out of the study or discontinue OIT prior to undergoing the Exit DBPCFC will be considered treatment failures (ie, Missing = Failure).

Fisher's exact test will be used to test the treatment difference for desensitization and exact CIs will be constructed as follows: (1) exact Clopper Pearson confidence limits will be used for the binomial proportion and (2) exact unconditional confidence limits based on the score statistic will be used for the difference in proportions.

9.2.2 Secondary Endpoints

The secondary endpoints are defined in Section 3.8, and a full description of the analyses planned for each will be provided in the SAP. A brief description of the planned analyses for the key secondary efficacy endpoints and other selected secondary endpoints is provided below.

9.2.2.1 Analysis of Key Secondary Endpoints

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

  The maximum symptom severity observed at any challenge dose in the Exit DBPCFC will be used for each subject in the primary analysis of this key secondary endpoint. Subjects without an Exit DBPCFC will have their maximum severity during the Screening DBPCFC used, which equates to no change from Screening.

  The number and percent of subjects by maximum severity at the Exit DBPCFC will be tabulated by treatment arm. The Cochran-Mantel-Haenszel statistic (with equally spaced scores) will be used to test for a treatment difference. The mean of the numerical values assigned to maximum severity by treatment group will also be reported.

  As supportive analyses, the analysis of maximum severity of symptoms during the Exit DBPCFC will be repeated for the maximum severity observed in the DBPCFC at

any dose up to a maximum challenge of 600 mg. The analysis will be repeated up through a maximum challenge of 300 mg, 100 mg, 30 mg, 10 mg, and 3 mg.

The key secondary efficacy endpoints will be tested in the ITT population in the hierarchical order specified above. Each comparison will be evaluated for statistical significance (two-sided $p < 0.05$) only if all of the preceding tests (not including supportive tests) in the hierarchy and the primary analysis of the primary endpoint are statistically significant in favor of AR101. The ITT population will be used as the primary population for analysis of key secondary endpoints. This closed testing procedure maintains the overall Type I error rate at 0.05 (EMEA CPMP, 2002; Cook et al, 2008). If any of the preceding tests are not significant, the p-value will be displayed for informational purposes only.

9.2.2.2 Analysis of Other Selected Secondary Endpoints

If all of the key efficacy secondary endpoints are found to be statistically significant, statistical testing of the other secondary efficacy endpoints will continue in the order that they are listed in Section 3.8.1.2 according to the same hierarchical closed testing procedure used for the key efficacy secondary endpoints. The other secondary endpoints are included in the overall hierarchical testing procedure. However, these endpoints are considered supportive in nature to the primary and key secondary endpoints.

Those secondary efficacy endpoints relating to the outcome of the Exit DBPCFC are described below. The statistical methods used for testing the remaining secondary efficacy endpoints are described in the SAP.

- Maximum dose achieved with no or mild symptoms at Exit DBPCFC: The probability estimates for tolerating each challenge dose or higher of the Exit DBPCFC will be calculated based on the discrete hazards model in the ITT population with terms for treatment group effect and the MTD at the Screening DBPCFC (baseline) in the $\log_{10}$ scale (Chinchilli et al, 2005). Following Chinchilli for the PRACTALL consensus report, the extreme value hazard function will be used for the discrete-time hazard function and the model will be fit with logistic regression with the complementary log-log link function. Subjects with no dose eliciting response at the 1000 mg single dose (2043 mg cumulative) will be censored at that dose. The probability estimates for each dose level will be tabulated by treatment group based on least-squares mean estimates from the above model. The values for MTD for subjects who do not undergo the Exit DBPCFC will be imputed using the maximum doses of peanut protein tolerated in their Screening DBPCFC. The treatment effect hazard ratio and its 95% CI and p-value will be based on the Wald statistic.
- Change from baseline in MTD of peanut protein at DBPCFC: Analyses of change from baseline MTD will be performed using change calculated on the $\log_{10}$ scale. An ANCOVA model of change from baseline MTD at Exit DBPCFC ($\log_{10}$ mg) will be fit with terms for treatment group and the MTD at baseline ($\log_{10}$ mg). The values for MTD for subjects who do not undergo the Exit DBPCFC will be imputed using the MTD of peanut protein in their Screening DBPCFC. The baseline adjusted least-squares means with 95% CIs by treatment group and for the treatment group

difference will be tabulated. The p-value is based on the F-test for treatment group effect adjusted for the MTD at baseline (log_{10} mg). Residuals for ANCOVA will be assessed for non-normality using the Shapiro-Wilk test. If significant at the 0.05 level, then the Wilcoxon rank sum statistic will be used to test for a treatment group difference to examine the robustness of the ANCOVA F-test.

9.2.3 Supportive Analyses of Primary and Secondary Endpoints

All analyses described in Sections 9.2.1 and 9.2.2 will be repeated in the Completer population and PP population (the latter, if sufficiently different). Sensitivity analyses, using different methods to handle missing data, will be described in the SAP.

9.3 Subject and Demographic Data

9.3.1 Study Disposition

The number and percentage of subjects screened, enrolled, randomized, completed and discontinued, entered and completed each study period, and in each analysis population will be summarized by treatment group and overall. Reasons for discontinuation from the study will be summarized by treatment group and overall. Total duration on treatment and total duration on study will also be summarized.

9.3.2 Baseline Characteristics and Demographics

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

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

9.3.3 Use of Medications

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

9.4 Sample Size and Power Calculations

The sample size for the study, approximately 160 subjects randomized 3:1 (AR101:placebo), has sufficient power to detect a treatment effect for the primary efficacy analysis. In Study ARC001, the placebo group response rate (95% CI) in the ITT population was 19% (7%, 39%) and 0% (0%, 13%) at 443 mg and 1043 mg cumulative peanut, respectively. Subjects were enrolled in Study ARC001 if at the Screening DBPCFC they expressed DLS at ≤ 144 mg cumulative peanut protein whereas in Study ARC010 they will be enrolled if they express DLS ≤ 443 mg cumulative peanut protein. Extrapolating to Study ARC010, where the primary efficacy endpoint is response rate in the ITT population at 2043 mg cumulative peanut protein, the placebo response rate is assumed to be at most 15%. With these considerations, a sample size of 120 AR101 and 40 placebo subjects and a 15% placebo response rate, there is at least 80% power to detect a response rate of 39% or higher in the

AR101 group using Fishers exact test with a 0.05 two-sided Type I error rate. Under the same assumptions, there is at least 90% power to detect a response rate of at least 43% in the AR101 group.

10. IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 Electronic Data Capture System

Data collection will occur via an EDC system to allow easy access to enrollment 24 hours a day, 7 days a week. As data are entered, they are validated through range and within-form consistency checks. The investigator must ensure that all CRFs are completed in a timely fashion for all subjects at his or her site.

10.2 Certification in the Use of EDC System

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

10.3 Data Management

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

10.4 Access to Data

The investigational sites shall periodically permit authorized representatives of the Study sponsor and/or regulatory health authorities to examine clinical records and other source documents for the purpose of safety monitoring, quality assurance reviews, audits, and evaluation of the study progress throughout the entire study period. The investigator is required by law and applicable guideline (21 CFR 312.62, EU Clinical Trials Directive 2001/20/EC, and ICH E6) to keep accurate case records for at least 2 years after 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 regulation.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Statement of Compliance

This study will be conducted using current Good Clinical Practice (GCP), as delineated in the United States CFR – 21 CFR Parts 50, 54, and 312 and in the ICH GCP, national and international regulations and directives as appropriate, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent/assent documents will be reviewed and approved by an appropriate IRB/EC and the applicable regulatory health authority of the country in which Study ARC010 is conducted. Any amendments to the protocol must also be approved by the sponsor, DSMC, and IRB/EC and

submitted to the applicable regulatory health authorities before they are implemented. Any amendments to the consent materials must also be approved by the Aimmune and the IRB/EC before they are implemented.

11.2 Informed Consent/Assent

The informed consent/assent form is a means of providing information about the study to a prospective adult subject or a pediatric subject's parent/guardian and allows for an informed decision about participation in the study. Because the study population will comprise only subjects 4 to 17 years of age, parents or legal guardians will be asked to read, sign, and date a consent form before a child enters the study, undergoes any study-specific procedures, or takes IP. Children will sign an assent as appropriate. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The informed consent/assent form will be evaluated for revision whenever the protocol is amended or new safety information becomes available. A copy of the informed consent/assent will be given to a prospective pediatric subjects' parent/guardian for review and subjects (and parent/guardian) will be allowed as much time as they need to consider their participation in the study. Where required by local authorities, both parents must sign the consent form before a child can be enrolled in the study. The attending physician will review the consent/assent and answer questions, as well as emphasize the need to avoid allergen exposure other than to IP, and the necessity to continue exposure to IP to maintain de-sensitization. The prospective pediatric subject's parent/guardian will be told that being in the study is voluntary and that he or she may withdraw his/her child from the study at any time, for any reason. The subject or subject's parent/guardian must be given a copy of the signed and dated consent/assent form. Written informed consent/assent must be in place prior to the commencement of any study-related procedures.

11.3 Privacy and Confidentiality

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

12. RESOURCE SHARING

All data derived from this study will be sent to the Reporting Center for storage and analysis. Subject data will be anonymized to maintain subject confidentiality. All-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 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, corrective actions will be developed by the site and implemented promptly as a result of protocol deviations.

13.1 Major Protocol Deviation (Protocol Violation)

A protocol violation is a deviation from the IRB/EC-approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with medical and ethical principles, and a serious or continuing non-compliance with federal, state, local, or institutional human subject protection regulations, policies, or procedures.

13.2 Non-Major Protocol Deviation

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

13.3 Reporting and Managing Protocol Deviations

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

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

Where necessary, the investigator can implement a deviation to the protocol in order 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 and the reasons for the deviation included with the documentation. In cases where protocol deviations lead to the protocol being amended, the amended protocol will be submitted to the relevant IRB/IEC and, where required, will also be submitted to the relevant regulatory authority.

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Appendix 1: Schedule of Events

Procedure	SCREEN-ING PERIOD (Day -27 to Day 0)	INITIAL ESCALATION PERIOD[a]		UP-DOSING PERIOD 20 to 40 Weeks Visits Every 2 Weeks (± 3 Days)			MAINTENANCE PERIOD 12 to 16 Weeks[b]	Early DC Visit[c] 14 to 16 Days after Last Dose	Exit Visit[d] 12 to 16 Weeks After First Dose of 300 mg/d	Unscheduled Visit[e]
		Day 1	Day 2	Up-dosing Visits	80 mg Up-dosing Visit	300 mg Up-dosing Visit[c]	Maintenance Visits			
Informed consent/assent[f]	X									
Inclusion/exclusion	X	X								
Review of Subject Eligibility Form[g]	X	X								
Randomize subject		X[h]								
Medical and allergy history	X									
Diet history (food allergen)	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Contraception review				X	X	X	X			X
Physical examination[i]	X	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X
Spirometry (FEV_1) and/or PEFR[k]	X		X					X	X	X
PEFR[l]		X		X	X	X	X			X
Asthma assessment[m]	X				X	X		X	X	X
FAQLQ & FAIM questionnaire[n]	X							X	X	
TSQM-9[o]								X	X	
Exit questionnaire[o]								X	X	
Palatability questions[p]								X	X	
Serum pregnancy test[q]	X									
Urine pregnancy test[q]					X	X		X	X	X
Blood draw (CBC/ immunology)[r]	X					X		X	X	X
Optional additional blood draw for exploratory immune cell characterization[s]	X					X		X	X	
SPT	X					X		X	X	X

Procedure	SCREEN-ING PERIOD (Day -27 to Day 0)	INITIAL ESCALATION PERIOD[a]		UP-DOSING PERIOD 20 to 40 Weeks Visits Every 2 Weeks (± 3 Days)			MAINTENANCE PERIOD 12 to 16 Weeks[b]	Early DC Visit[c] 14 to 16 Days after Last Dose	Exit Visit[d] 12 to 16 Weeks After First Dose of 300 mg/d	Unscheduled Visit[e]
		Day 1	Day 2	Up-dosing Visits	80 mg Up-dosing Visit	300 mg Up-dosing Visit[c]	Maintenance Visits			
Epinephrine auto-injector check[t]	X									
DBPCFC (2 parts within 7 days)	X[u]								X[v]	
Peanut / food allergy education	X				X	X				X
Reminder to avoid peanut	X	X	X	X	X	X	X			X
Monitor AEs and allergic symptoms[w]	X[x]	X	X	X	X	X	X	X[w]	X[w]	X
Administration of OIT at site		X	X	X	X	X	X			X
Dispense / return unused IP			X[y]	X	X	X	X			X
Monitor for dosing compliance				X	X	X	X			X
Home dosing instruction			X		X	X	X[z]			X
Telephone follow-up[aa]			X	X	X	X				X
Treatment unblinding[bb]									X	

Abbreviations: AEs = adverse events; DBPCFC = double-blind, placebo-controlled food challenge; DC = discontinuation; FAIM = food allergy independent measure; FAQLQ = food allergy-related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; IP = investigational product; Maint, maintenance; OIT = oral immunotherapy; PEESS v2.0 = Pediatric Eosinophilic Esophagitis Symptom Scores, version 2.0; PEFR = peak expiratory flow rate; SPT = skin prick test; TSQM-9 = Treatment Satisfaction Questionnaire for Medication.

a) Initial Escalation is scheduled within 10 days after the Screening DBPCFC and must occur within 6 weeks of signing the consent/assent form. Day 1: Escalation to at least 3 mg or 6 mg, as tolerated (subjects who cannot tolerate 3 mg are escalation failures). Day 2: Confirm tolerance of 3 mg. Day 2 is the next consecutive day after Day 1 unless unforeseen circumstances (eg, intercurrent illness) create a safety risk (Section 6.3.2.1).

b) The Maintenance Period lasts for approximately 12 weeks but may be extended up to a maximum of 16 weeks or to a maximum study duration of 56 weeks, whichever is shorter (Section 6.3.3.3). There is a ± 3-day visit window for all visits in the Maintenance Period. The first Maintenance Visit is 2 weeks after the 300 mg Up-dosing Visit. The next 3 visits are at 6, 10, and 12 weeks after the 300 mg Up-dosing Visit. If at 12 weeks after the 300 mg Up-dosing Visit the subject has maintained a dose of 300 mg/d for approximately 12 weeks, without the use of symptomatic therapy for the last 4 weeks, the Exit Visit will be performed. If that is not the case, then the subject will continue in the study for up to 4 more weeks of 300 mg/d dosing before proceeding to the Exit Visit.

c) Early Discontinuation Visit applies to subjects who fail initial escalation or up-dosing or prematurely discontinue study treatment.

d) Exit Visit applies to subjects who tolerate 300 mg/d and are maintained on this dose for approximately 12 weeks (up to a maximum of 16 weeks).

e) Any or all procedures performed at Up-dosing Visits and spirometry may be performed at Unscheduled Visits.

f) Before any other study procedures.

g) Subject Eligibility Form completed by the site at Screening is reviewed by the medical monitor to confirm whether subject may be randomized, and approval must be verified before randomization.

h) Randomization occurs once subject eligibility has been confirmed by the medical monitor (following the medical monitor's review of the Subject Eligibility Form).

i) Physical examination including height and weight at: Screening, Initial Escalation Day 1 (not height), and the Up-dosing 80 mg and 300 mg, Exit, and Early Discontinuation Visits. Symptom-directed physical examination (at investigator's discretion [ie, not necessarily include height and weight])) at: Initial Escalation Day 2, Up-dosing Visits (except the 80 mg and 300 mg Up-dosing Visits), and Maintenance Visits.

j) Vital signs: blood pressure, pulse rate, and body temperature. Screening, Exit, and Early Discontinuation Visits: Where a DBPCFC occurs at these visits, vital signs are measured just before each DBPCFC challenge dose or at 15-20 minutes post-dose, if the between challenge dosing interval is prolonged. Initial Escalation Days 1 and 2: pre-dose and post-dose (within 15-30 minutes post-dose, at 30 minutes thereafter, and for the duration of the post-dose observation period). Up-dosing Visits: pre-dose and post-dose (within 15-30 minutes post-dose, and at 15-30 minute intervals thereafter for the post-dose observation period). Maintenance Visits: As for Up-dosing except post-dose measurements do not need to continue beyond 30 minutes unless the post-dose observation period is extended beyond 30 minutes.

k) Spirometry (FEV_1) and/or peak expiratory flow rate (PEFR): conducted prior to the start of the DBPCFC, 3 attempts should be made with the best value recorded. PEFR should be measured at the same time of day for each visit assessment (eg, morning, afternoon, evening).

l) PEFR: 3 attempts should be made with the best value recorded. PEFR should be measured at the same time of day for each visit assessment (eg, morning, afternoon, evening). If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.

m) For subjects with asthma only: evaluation of asthma severity using the 2007 NHLBI Criteria (Appendix 2) and the Asthma Control Test questionnaire.

n) FAQLQ and FAIM questionnaires to be completed prior to the Screening DBPCFC and after completion of the Exit DBPCFC and the subject's treatment assignment has been unblinded.

o) TSQM-9 and Exit questionnaire to be completed after completion of the Exit DBPCFC and the subject's treatment assignment has been unblinded.

p) Palatability questions to be answered before the Exit DBPCFC.

q) For females of childbearing potential only. To be performed and results obtained prior to DBPCFC, where applicable.

r) Blood draw for IgE and IgG4 is to be drawn prior to DBPCFC.

s) Separate informed consent required. No more than 2.5 mL/kg may be drawn, up to a maximum of 70 mL on any one study day. Multiple attempts to obtain blood, and repeat samples can be collected where necessary for damaged samples or safety reasons.

t) It must be verified that the subject has an epinephrine auto-injector prior to the subject leaving the clinic on day 1 of the Screening DBPCFC.

u) At the end of the Screening period, eligible subjects who satisfy all other Screening requirements, will undergo a DBPCFC a maximum challenge dose of 300 mg (444 mg cumulative).

v) Subjects who up-dose to 300 mg and maintain this dose for approximately 12 weeks without symptomatic therapy for at least the last 4 weeks will undergo the Exit DBPCFC at the end of Maintenance Period to a maximum challenge dose of 1000 mg (2043 mg cumulative).

w) AEs and allergic symptoms will be collected from the point of signing the ICF until 30 days after the subject completes study treatment. Each event should be evaluated from the point of onset until the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.
Subjects with ongoing AEs at early discontinuation or study exit will have safety follow-up for at least 30 days or until the AEs resolve or stabilize, whichever is last (Section 4.3.2). Subjects who have gastrointestinal AEs with prolonged disruption of dosing or who discontinue treatment due to gastrointestinal AEs will have safety follow-up for 6 months or until the chronic/recurrent gastrointestinal AE resolve or stabilize, whichever is last. These subjects will complete the PEESS v2.0 questionnaire while symptomatic, at the time of treatment discontinuation, and monthly for 6 months during safety follow-up (Section 7.3.3.2). Subjects may complete the PEESS v2.0 at home and send it to the clinic, or at the clinic if they have monthly clinic visits. Subjects who discontinue treatment due to gastrointestinal AEs will be asked to return to the clinic for evaluation monthly for at least 6 months (if asymptomatic, telephone follow-up may be appropriate per investigator discretion).

x) Assessment of signs and symptoms of allergic reaction is to be performed at the same time points vital signs are measured during the DBPCFC procedures.

y) The first dose of home dosing study medication (3 mg/d) is taken by the subject on the day following Initial Escalation Day 2 (ie, Day 3).

z) The first visit of the Maintenance Period only.

aa) Phone calls will occur 1 day after Initial Escalation Day 2 and each Up-dosing Visit to inquire about allergic symptoms and promote dosing compliance.

bb) Subject will be unblinded after the Exit DBPCFC is completed, all major data queries are resolved, and the follow-on study ARC008 is available at the study site.
If ARC008 is not yet available the study site, subjects may continue blinded study treatment and have clinic visits every 4 weeks in ARC010 until ARC008 is available.
Subjects who complete 12 weeks of maintenance and do not tolerate 300 mg peanut protein at the Exit DBPCFC will not continue blinded study treatment in ARC010.

Appendix 2: Evaluation of Asthma

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

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

[a] Normal FEV_1/FVC: 8-19 years = 85%

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

Criteria for Suspected Diagnosis

Anaphylaxis is likely when any 1 of the 3 following sets of criteria (EAACI - Muraro et al, 2007) 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 (minute to hour):
   - 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. Low systolic BP for children is defined as < 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 × age]) from 1 to 10 years; and < 90 mmHg from age 11 to 17 years.

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

Criteria for Severity Grading (Muraro et al, 2007)

Staging System of Severity of Anaphylaxis	
Stage	**Defined by**
1. *Mild* (skin 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

Appendix 4: Allergic Reaction Severity Grading

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

Table A4: CoFAR Specific Grading System for Allergic Reactions

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

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

For an episode of anaphylaxis to be considered an SAE, the sponsor advises that the event satisfy 1 of the outcome-based definitions of SAE specified in Section 7.3.1.1, with the stipulations (denoted in *italics*) indicated. These stipulations follow from, and are consistent with, the criteria for DSMC reporting (Section 7.9.3):

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, as defined in Appendix 3 and of a Grade 4 allergic reaction, as defined in Table A4 of Appendix 4.*
3. Inpatient hospitalization or prolongation of existing hospitalization: *The hospital admission should not have been solely for the sake of providing an extended period of observation, as, for example, might be implemented to watch for a delayed or biphasic reaction.*
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: *No further stipulation*.
5. Congenital abnormality or birth defect: *No further stipulation*.
6. Important medical event that may not result in 1 of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent 1 of the outcomes listed in the above definition of serious event:
    - 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 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.