
# ARC007

# Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES)

## Clinical Study Protocol

| Version | Date |
|---|---|
| **Original Protocol** | **21 October 2016** |
| **Amendment 1.0** | **28 February 2017** |
| **Amendment 2.0** | **27 September 2017** |

**Aimmune Therapeutics, Inc.**

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**CLINICAL STUDY PROTOCOL ARC007**
**Sponsor Personnel**

| | |
|---|---|
| **Clinical Lead, Clinical Operations** | Freddy Byrth<br>Aimmune Therapeutics, Inc. |
| **Chief Medical Officer** | Daniel C. Adelman, MD<br>Aimmune Therapeutics, Inc. |
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## Sponsor Protocol Approval

| | |
|---|---|
| Protocol ARC007 | Version: Amendment 2.0<br>Date: 27 September 2017 |
| Sponsor: Aimmune Therapeutics, Inc. | |
| Title: Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES) | |

*I have read protocol ARC007, Amendment 2.0, and I approve it. I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigators and all other Investigators of all relevant information that becomes available during the conduct of this study.*

_____ _____

Daniel C. Adelman, MD Date
Chief Medical Officer

## Principal Investigator Protocol Acknowledgement

| | |
|---|---|
| Protocol ARC007 | Version: Amendment 2.0<br>Date: 27 September 2017 |
| IND: 15463 | |
| Title: Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES) | |

*I have read Clinical Study Protocol ARC007, Amendment 2.0. 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(R1) 10 June 1996, and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, state, and federal requirements.*

_____

Principal Investigator (Print)

_____ _____

Principal Investigator (Signature) Date

| Protocol ARC007 Amendment 2.0 Synopsis | |
|---|---|
| **Title** | **REAL-WORLD AR101 MARKET-SUPPORTING EXPERIENCE STUDY IN PEANUT-ALLERGIC CHILDREN AGES 4 TO 17 YEARS** |
| **Short Title** | RAMSES |
| **Clinical Phase** | 3 |
| **IND** | 15463 |
| **IND Sponsor** | Aimmune Therapeutics, Inc. |
| **Number of Subjects** | Up to 500 peanut-allergic children will be randomized in a 2:1 ratio to AR101, a pharmaceutical-grade peanut allergen formulation, or placebo. The study population will consist of children aged 4 to 17 years, inclusive. Randomization will be stratified by age group (4 to 11 years and 12 to 17 years of age). |
| **Objectives** | The primary objective is to assess the safety and tolerability of AR101 when used in a characterized oral desensitization immunotherapy (CODIT)™ regimen for approximately 6 months in peanut-allergic children.<br>The secondary objectives are to characterize the frequency of all treatment-related adverse events (AEs) by study period, especially those of interest (defined in Section 7.3.4 of the protocol), and AR101's effect on asthma control and immune parameters. |
| **Study Design** | This is a multicenter, randomized, double-blind, placebo-controlled safety study of AR101 using the CODIT regimen in peanut-allergic children. The study will consist of a screening phase and a double-blind treatment phase that includes an initial 2-day escalation period and an up-dosing period. Subjects will be approached at the time of enrollment about donating saliva and additional blood samples to support exploratory biomarker analyses in a sub-study. Participation in this sub-study is voluntary and requires signing separate consent and assent documents.<br>After completion of the up-dosing period, all study exit procedures, and treatment unblinding, subjects who received AR101 may participate in an open-label maintenance trial, known as Study ARC011; subjects who received placebo will be offered up-dosing and maintenance treatments with AR101 in Study ARC008. For subjects participating in follow-on studies, both follow-on protocols must be activated at the study site before subjects can complete all of the required ARC007 study exit procedures. Certain procedures (specifically, completion of questionnaires) and treatment unblinding will be completed at a later unscheduled visit if necessary to accommodate institutional review board (IRB) review of the follow-on protocols and shipment of open-label AR101. Additionally, all major data queries must be resolved before subjects complete exit procedures and proceed to a follow-on study. Subjects will remain on blinded study treatment and have an unscheduled visit every 4 weeks or sooner until all exit requirements are met.<br>The Screening/Baseline Period is up to 21 days. Eligible subjects will be randomized in a 2:1 ratio to receive escalating doses of either AR101 or placebo, in 2 phases. Following a 2-day initial escalation phase, up-dosing will be a minimum of 20 weeks to a maximum of 40 weeks in duration in order to achieve the 300 mg/d dose level. Subjects reaching this dose will continue in the study for an additional 2 weeks to ensure tolerability of the 300 mg/d dose before proceeding to the exit visit. If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study. |

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| | For subjects terminating early for related and GI AEs, additional observational follow-up will occur monthly in clinic or by phone for up to 6 months or until the symptoms have resolved or stabilized, or the Investigator deems them to be irreversible, according to details described further in Section 6.5 of the protocol.<br>Beginning at signed informed consent and assent as age-appropriate, all AEs 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 Exit or Early Discontinuation Visit, whichever comes first, with the exception of gastrointestinal (GI) AEs, detailed further below. 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 may be required. Subjects who discontinue dosing prematurely due to chronic/recurrent GI AEs will complete the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)$^{TM}$ version 2.0 questionnaire and return to the clinic for evaluation monthly for at least 6 months (if the subject is asymptomatic, telephone follow-up with an Investigator may substitute for in-clinic visit, at the Investigator's discretion). If chronic/ recurrent GI AEs persist beyond 6 months, subjects are to continue to be followed with monthly clinic visits (telephone follow-up with an Investigator may substitute for in-clinic visit, at the Investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management or the Investigator deems them to be irreversible. The protocol provides additional specific guidance about symptomatic medical management and referrals to a gastroenterologist, as necessary, in Section 7.3.4.2 of the protocol.<br>A Data Safety Monitoring Committee has been established to monitor the study for safety.<br>Subjects who received AR101 and completed ARC007 will have the option to participate in the ARC011 study. The ARC011 study is an open-label safety extension study of ARC007 to evaluate the safety and tolerability of 300 mg/d maintenance dosing for up to 6 months. After completing Study ARC011, subjects will be able to proceed to ARC008 for further maintenance dosing.<br>Subjects who received active treatment but did not reach 300 mg/d within 40 weeks or were unable to tolerate 300 mg daily for 2 weeks by 48 weeks after Day 1 will not be eligible for enrollment in ARC011 or ARC008.<br>Subjects who received placebo and completed ARC007 will be offered up-dosing and maintenance treatment with AR101 in the ARC008 study. In ARC008, these subjects will undergo an escalation schedule identical to that for active subjects in the ARC007 study and then continue on maintenance dosing at 300 mg/d.<br>All subjects who enter ARC008 will be allowed to continue receiving AR101 until it becomes commercially available or the development program is terminated. |
| **Study Duration** | Screening/baseline for up to 21 days.<br>Dosing typically for 22 to 48 weeks, unless double-blind treatment is extended for subjects waiting for activation of follow-on protocols.<br>Up to 6 months (or more) additional observational follow-up for subjects terminating early for GI AEs. |

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| **Primary Endpoint** | The primary endpoint of this study is the frequency of treatment-emergent AEs, including serious AEs, during the overall study period. |
| **Secondary Endpoints** | Secondary Endpoints<br>• Frequency of premature discontinuation of dosing due to AEs<br>• Frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs<br>• Proportion of chronic / recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing<br>• Frequency of allergic reaction (hypersensitivity) AEs occurring during up-dosing, normalized for duration of treatment<br>• Frequency of anaphylaxis as defined in the protocol<br>• Frequency of use of epinephrine as a rescue medication<br>• Frequency of accidental ingestions of peanut and other allergenic foods and severity of any resultant reactions<br>• Assessment of asthma control using the Asthma Control Test (ACT) questionnaire and frequency of use of asthma rescue medication (short acting beta-agonists) in subjects with asthma |
| **Exploratory Endpoints** | Exploratory Endpoints<br>• Changes in peanut-specific and peanut component-specific serum immunoglobulin E (IgE) and immunoglobulin G subclass 4 ($IgG_4$) levels<br>• Changes in peanut skin prick test (SPT) mean wheal diameter<br>• Changes in Total Nasal Symptom Score in subjects with allergic rhinitis<br>• Changes in scores of the food allergy related quality of life questionnaire (FAQLQ) and food allergy independent measure (FAIM) questionnaire |
| **Investigational Product and Dispensing** | AR101 or Placebo<br>AR101 is a characterized, oral biological drug product containing the protein profile found in peanuts. AR101 doses will ascend per the dosing regimen outlined below. Investigational product (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. Trained investigational site personnel will dispense the IP to the subject or the subject's parent or guardian in a manner consistent with the assigned dose level. Investigational product will be dispensed in a double-blinded fashion according to subject randomization number, using an interactive voice/web response system.<br>All IP will be stored at the site in a secure location and kept refrigerated between 2°C and 8°C. |
| **Inclusion Criteria** | 1. Age 4 to 17 years, inclusive<br>2. A history of physician-diagnosed IgE-mediated peanut allergy that includes the onset of characteristic allergic signs and symptoms within two hours of known oral exposure to peanut or a peanut-containing food. While IgE-mediated reactions have varied presentations, in general, characteristic allergic signs and symptoms are objective and affect the target organs of the skin, GI tract, upper and/or lower respiratory tract, cardiovascular system, or a combination (Appendix 2 of the protocol). |

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| | 3. Mean peanut wheal diameter on SPT of ≥ 8 mm greater than the negative saline control at Screening<br>4. Serum IgE to peanut of ≥ 14 $kU_A/L$ at Screening<br>5. Written informed consent from the subject's parent/guardian<br>6. Written assent from the subject as appropriate (eg, above the age of 7 years or the applicable age per local regulatory requirements)<br>7. Use of effective birth control by sexually active female subjects of childbearing potential |
| **Exclusion Criteria** | 1. Subjects in whom the clinical diagnosis of peanut allergy is uncertain<br>2. History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension (see Section 5.10 of the protocol)<br>3. Use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, or tricyclic antidepressants (see Section 5.10 of the protocol)<br>4. History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of screening<br>5. History of eosinophilic esophagitis (EoE), other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease, symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"), or recurrent GI symptoms of undiagnosed etiology<br>6. History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema<br>7. Severe persistent asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] Criteria Steps 5 or 6, see Appendix 3 of the protocol)<br>8. Mild or moderate persistent asthma (2007 NHLBI Criteria Steps 1 to 4), if uncontrolled or difficult to control as defined by any of the following:<br>a. 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<br>b. Inhaled corticosteroid (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICSs based on NHLBI dosing chart); or<br>c. One hospitalization in the past year prior to screening for asthma; or<br>d. Emergency room visit for asthma within 6 months prior to screening<br>9. 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:<br>a. History of daily steroid dosing for > 1 month during the past year; or<br>b. 1 steroid course in the past 3 months; or<br>c. > 2 steroid courses in the past year ≥ 1 week in duration<br>10. 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<br>11. Inability to discontinue antihistamines 5 half-lives before the screening SPT and initial day of escalation |

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| | 12. Lack of an available palatable vehicle food to which the subject is not additionally allergic<br>13. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector<br>14. Use of omalizumab or any other monoclonal antibody therapy within the 6 months prior to screening or any current immunomodulatory therapy besides aeroallergen or venom immunotherapy or corticosteroids (see also Section 5.10 of the protocol)<br>15. Having received at least one dose of AR101 in a previous Aimmune or Allergen Research Corporation study<br>16. Use of other forms of peanut immunotherapy (eg, oral, sublingual, epicutaneous) within 6 months prior to screening<br>17. Participation in another clinical trial within 30 days or 5 half-lives of the IP, whichever is longer, prior to randomization<br>18. Concurrent administration of "build-up phase" of immunotherapy to another allergen (ie, subject has not reached maintenance dosing)<br>19. Pregnancy or lactation<br>20. Having the same place of residence as another subject in any AR101 study |
| **Treatment Description** | Screening/Baseline: All subjects will undergo the screening procedure outlined in Section 6.2 of the protocol and eligible subjects will be randomized 2:1 to active treatment with AR101 or placebo.<br>Initial Escalation (2 days): Eligible subjects will be randomized and initiate CODIT 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 ≥ 3 mg dose on Day 1 will be considered escalation failures and will be discontinued. Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on the following day, Day 2. Subjects who tolerate this confirmatory dose will enter the Up-Dosing Period. Subjects who do not tolerate this confirmatory dose will be discontinued. Initial escalation failures, either on Day 1 or Day 2, will be asked to return to the clinical research center (CRC) 14 days following the last dose of IP to undergo an Early Discontinuation Visit.<br>Up-dosing: Subjects will receive IP starting at a dose of 3 mg once daily and will gradually escalate every 2 weeks to a maximum of 300 mg once daily, according to the Up-Dosing Schedule (see Table 2 of the protocol). Subjects who are unable to escalate to 300 mg within 40 weeks or who are unable to tolerate 300 mg daily for 2 weeks by 48 weeks after Day 1 will be considered escalation failures.<br>Subjects able to escalate to 300 mg/d will continue taking the 300 mg dose for an additional 2 weeks and then exit the study, providing all exit requirements are met. If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 total weeks since Day 1 to ensure tolerability prior to exiting the study.<br>Unblinding of each subject's treatment assignment will occur at study completion per the conditions stated previously, and the subjects will have the option to enter a rollover study depending on their ARC007 treatment |

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| | assignment: ARC011 for AR101-treated subjects, and ARC008 for those receiving placebo.<br>The first dose at each new dose level for up-dosing 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). Subsequent doses will be dispensed to the subject or parent/guardian and administered at home.<br>All up-dosing activities will be performed under direct observation. Doses may be adjusted for tolerability or inter-current illness by the Investigator, except no down-dosing below 3 mg/day is allowed. Up-dosing period may thereby be extended to a maximum of 40 weeks in order to reach 300 mg and should not exceed this period. Those subjects who reach the target dose of 300 mg/d of IP will take this dose for an additional 2 weeks. Subjects unable to escalate to 300 mg within 40 weeks will be considered escalation failures. Subjects able to escalate to 300 mg will continue taking the 300 mg dose for an additional 2 weeks to ensure tolerability prior to exiting ARC007. Non-responder subjects will be asked to return to the CRC 14 days following the last dose of IP to undergo an Early Discontinuation Visit.<br>Once all conditions are met for enrollment in the appropriate follow-on study, treatment assignments will then be unblinded, and subjects will have the option to enroll in ARC011 or ARC008. Subjects who fail to reach the 300 mg/d dose of IP within 40 weeks will be discontinued from ARC007 and will be ineligible to enroll in ARC011 or ARC008.<br>Further details can be found in Section 6 of the protocol. |
| **Study Procedures** | The following procedures will be performed according to the scheduled visits tabulated in the Schedule of Events for ARC007 (Appendix 1 of the protocol):<br>• Informed consent (and assent, as age appropriate)<br>• Inclusion/exclusion criteria<br>• Medical/allergy history<br>• Diet history<br>• Concomitant medications<br>• Physical examination, including height and weight<br>• Vital signs (blood pressure, pulse rate, temperature)<br>• Spirometry ($FEV_1$) in children ≥ 6 years<br>• Peak expiratory flow rate<br>• Pregnancy test for sexually active females of childbearing potential<br>• Blood draw for peanut-specific IgE and $IgG_4$<br>• Complete blood cell count, obtained with the same venipuncture as the blood draw for the immunoglobulin assays<br>• Additional blood samples for optional exploratory immunologic studies. These can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays (separate informed consent required).<br>• Optional blood sample(s)<br>• Optional collection of saliva sample for exploratory biomarker development (separate informed consent required)<br>• SPT<br>• Randomization and IP administration<br>• Dispensing of IP for home-dosing/return of unused IP |

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| | • AE monitoring<br>• Monitoring for dosing compliance<br>• Assessment of asthma control using the ACT questionnaire and frequency of asthma rescue medication use in subjects with asthma<br>• PEESS v2.0 questionnaire (for subjects with GI AEs that interrupt dosing)<br>• Peanut allergy teaching<br>• Telephone follow-up<br>• Completion of the FAQLQ and the FAIM questionnaire.<br>• Completion of the Total Nasal Symptom Score in subjects with allergic rhinitis |
| **Statistical Considerations** | ARC007 is a safety study that will add critical placebo-controlled observations to the ongoing safety database of AR101. As such, there are no efficacy endpoints in the study, no specific efficacy-related hypotheses to be tested, and thus no prospective sample size calculations performed related to the clinical effectiveness of AR101 treatment versus placebo.<br>A sample size of up to 500 subjects, randomized in a 2:1 ratio to AR101 or placebo, along with subjects enrolled in other studies in the clinical program will provide a sufficient number of subjects to fulfill the regulatory requirement for data on at least 600 subjects dosed for 6 months at 300 mg/d.<br>Data will be summarized using descriptive statistics and will be displayed by treatment group. No specific hypothesis testing or comparisons between the treatment groups is planned for this study. Further details on the analytical approach and any exploratory comparisons between treatments will be provided in the statistical analysis plan. See Section 9 of the protocol for further information. |

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## List of Appendices

# List of Abbreviations

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| AAAAI | American Academy of Allergy, Asthma & Immunology |
| ACE | angiotensin-converting enzyme |
| ACT | Asthma Control Test |
| AE | adverse event |
| AEI | adverse event of interest |
| AR101 | characterized peanut allergen |
| ARB | angiotensin-receptor blocker |
| BP | blood pressure |
| CBC | complete blood cell count |
| CFR | US Code of Federal Regulations |
| CODIT | characterized oral desensitization immunotherapy |
| CoFAR | Consortium of Food Allergy Research |
| CRC | clinical research center |
| CRF | case report form |
| DBPCFC | double-blind, placebo-controlled food challenge |
| DSMC | Data Safety Monitoring Committee |
| EAACI | European Academy of Allergy and Clinical Immunology |
| EC | ethics committee |
| EDC | electronic data capture |
| EGD | esophagogastroduodenoscopy |
| ELISA | enzyme-linked immunosorbent assay |
| EoE | eosinophilic esophagitis |
| ER | emergency room |
| FAIM | food allergy independent measure (questionnaire) |
| FAQLQ | food allergy quality of life questionnaire |
| FDA | US Food and Drug Administration |
| $FEV_1$ | forced expiratory volume in 1 second |
| GCP | Good Clinical Practice |
| GERD | gastroesophageal reflux disease |
| GI | gastrointestinal |

| | |
|---|---|
| ICH | International Council for Harmonisation |
| ICF | informed consent form |
| ICS | inhaled corticosteroid |
| lgE | immunoglobulin E |
| $lgG_4$ | immunoglobulin G subclass 4 |
| IND | Investigational New Drug |
| IP | investigational product |
| IRB | institutional review board |
| ITT | intent-to-treat |
| IV | intravenous |
| IXRS | interactive voice/web response system |
| NCI-CTCAE | National Cancer Institute 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 |
| PR | pulse rate |
| PRACTALL | PRACTical issues in ALLergology Joint United States/European Union |
| qPCR | quantitative polymerase chain reaction |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SOE | schedule of events |
| SPT | skin prick test |
| SVM | support vector machine |
| TEAE | treatment-emergent adverse event |

# 1. BACKGROUND AND RATIONALE

## 1.1 Background

Peanut allergy is a common and serious condition that disproportionately affects children and is associated with severe reactions, including life-threatening anaphylaxis. The prevalence of peanut allergy, like other food allergies, has been rising, and is now at high levels, affecting up to 2% of the population (Sicherer and Sampson 2014). The current standard of care in management of peanut allergy is a peanut-avoidant diet, along with education of the patient and family in the acute management of an allergic reaction, including ready access to self-injectable epinephrine. The burden of avoidance and the constant fear of accidental exposure negatively affect the health-related quality of life for patients and their families (Primeau et al, 2000; Avery et al, 2003; Sicherer et al, 2010; Anagnostou et al, 2014).

In addition, peanut-avoidant diets are complicated by the difficulty of interpreting food labels and the presence of undeclared or hidden allergens in commercially-prepared foods (Joshi et al, 2002; Altschul et al, 2001; Vierk et al, 2002). Accidental exposures are common, with 55 percent of food-allergic patients having at least 1 allergic reaction in a 5-year period (Sicherer et al, 1998).

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

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

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

## 1.2 Clinical Trials of AR101

### 1.2.1 ARC001 Trial

ARC001 was a multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic children and adults 4 to 26 years of age. ARC001 consisted of a screening period, including a screening double-blind placebo-controlled food challenge (DBPCFC), an initial escalation period, an up-dosing period, and a maintenance period, followed by an exit DBPCFC. The primary endpoint of ARC001 was the percentage of desensitization responders, defined as subjects tolerating 300 mg (443 mg cumulative) at the Exit DBPCFC.

A total of 56 subjects were randomized: 29 subjects to AR101 and 27 subjects to placebo. One subject in the placebo group withdrew consent after randomization and before treatment. The intent-to-treat (ITT) population thus comprised 55 subjects: 29 in the AR101 and 26 in the placebo arm. The 2 groups were overall well matched for baseline characteristics including baseline sensitivity in the Screening DBPCFC. Six subjects in the AR101 arm withdrew prior to the Exit DBPCFC.

In the ITT population, AR101 was statistically significantly superior to placebo, with 23 of 29 (79%) desensitization responders in the AR101 group as compared to 5 of 26 (19%) desensitization responders in the placebo group, resulting in a treatment difference of 60% ($P < 0.0001$ by Fisher's exact test). In the completer population (those subjects completing the Exit DBPCFC), 23 of 23 AR101 completers were desensitization responders, resulting in a treatment difference of 81% ($P < 0.0001$ by Fisher's exact test). At the time of the exit visit, the geometric mean for peanut-specific IgE levels were lower for the AR101 group compared with the placebo group; higher for the AR101 group compared with the placebo group for peanut-specific IgG4; and lower for the AR101 group compared with the placebo group for peanut-specific IgE/IgG4 ratio.

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 hypersensitivity (verbatim: anaphylaxis) related to treatment. One subject (4%) in the placebo group experienced an SAE of presyncope/hypersensitivity (verbatim: vaso-vagal reaction/anaphylaxis) related to the peanut protein in the Exit DBPCFC, not investigational product (IP). An additional subject experienced a prerandomization, non-treatment-emergent SAE of hypersensitivity (verbatim: slow developing anaphylaxis or biphasic reaction) following the Screening DBPCFC. No placebo-treated subject had an adverse event leading to discontinuation. A total of 4 AR101-treated subjects (14%) experienced an adverse event that led to permanent discontinuation of study treatment. One subject discontinued due to a treatment-related adverse event of eosinophilic esophagitis (EoE), 2 subjects each discontinued treatment due to a treatment-related adverse event of vomiting and 1 subject discontinued due to an adverse event of stomach pain. Two additional AR101-treated subjects withdrew from the study prematurely due to withdrawal of consent or investigator decision. Both subjects also experienced gastrointestinal (GI) adverse events that likely contributed to their withdrawal from the study.

In summary, AR101 appeared to be generally well tolerated, and significantly 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 compared with placebo.

### 1.2.2 ARC002 Trial

All ARC001 placebo subjects who completed the ARC001 study were eligible for rollover into the open-label ARC002 protocol. All subjects on AR101 who passed the ARC001 Exit DBPCFC by tolerating ≥ 443 mg cumulative of peanut protein with no more than mild symptoms were also eligible to enter ARC002.

Group 1 included subjects who completed the placebo arm of ARC001 and consented to enroll in ARC002, crossing over to active treatment using the same dosing regimen used in ARC001, but in open-label fashion. After completion of the Up-dosing Phase, Group 1 subjects underwent a DBPCFC (to a maximum single dose of 600 mg of peanut protein, or 1043 mg of cumulative peanut protein). Subjects who did not tolerate the post-low-dose build-up phase DBPCFC at ≥ 443 mg cumulative were considered escalation failures and were discontinued from the study due to safety concerns. Those subjects who tolerated the DBPCFC at ≥ 443 mg cumulative of peanut protein entered an approximately 3-month (12- to 24-week) Plateau Phase of continued dosing at 300 mg/d.

Group 2 subjects who completed the active AR101 arm of ARC001 and consented to enroll into ARC002 went directly into the 300 mg/d, 3-month Plateau Phase of ARC002. Following completion of the 3-month Plateau Phase, all ARC002 subjects underwent a post-Plateau Phase DBPCFC (to a maximum single dose of 1000 mg of peanut protein, or 2043 mg cumulative).

Based on the total population of 26 Group 1 subjects receiving ≥ 1 dose of AR101, 76.9% of subjects tolerated 300 mg and 65.4% tolerated 600 mg. At the post-Plateau DBPCFC in 40 subjects in Groups 1 and 2, 100%, 90%, and 60% of the subjects tolerated a cumulative peanut protein dose of 443 mg, 1043 mg, and 2043 mg, respectively. These findings demonstrate the persistence of desensitization during daily maintenance treatment with AR101 at 300 mg/d, further supporting the primary endpoint selection in the Phase 3 trial ARC003. The findings also indicate that treatment with AR101 may achieve a maximum tolerated dose of food allergen substantially higher than the dose used for maintenance itself.

The overall profile of AEs observed in ARC002 is consistent with what was observed in ARC001 and with what has been reported in the literature for academic peanut oral OIT clinical trials. These findings continue to support the ongoing clinical development of AR101, and in particular, the safety and tolerability of low-dose maintenance treatment at 300 mg/d.

### 1.2.3 ARC003 Trial

ARC003 is an ongoing international, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in a characterized desensitization OIT regimen in peanut-allergic individuals. The study consists of a screening phase that includes a Screening

phase (including a 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 receive escalating doses of either AR101 or placebo, randomized in a 3:1 ratio. 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 ≥ 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 meets regularly at defined intervals.

### 1.3 Rationale for the Current Study

The rationale for the ARC007 study is to characterize the safety of AR101 in a broader population of children who are highly likely to have been diagnosed as being peanut allergic based on clinical features alone. To date, Aimmune's Phase 2 and Phase 3 randomized controlled trials have included a screening DBPCFC that is used to select a highly sensitive study population (those reacting at or before 100 mg of peanut protein during that challenge). This, in turn, has allowed recruitment of subjects with any value of skin prick test (SPT) or immunoglobulin E (IgE), since the DBPCFC establishes their baseline sensitivity. However, DBPCFCs are associated with a substantial risk of anaphylaxis both at screening and again at exit, especially in the placebo group. During North American screening for ARC003, 240 doses of epinephrine were administered to 457 subjects who reacted to the DBPCFC, 54 (12%) of whom had at least one severe symptom. Three subjects experienced anaphylaxis to the DBPCFC that met seriousness criteria (Vickery et al, 2017). In addition, mechanistic data suggest that the pre-randomization exposure to peanut required by the DBPCFC procedure may induce peanut-specific T cell activation and potentiate allergic inflammation detectable after the DBPCFC (Rust et al, 2017). This residual inflammation related to the screening food challenge may have unintended consequences affecting the safety and tolerability of the initial stages of the desensitization procedure.

Moreover, in the anticipated post-marketing clinical use of AR101, subjects would not be selected for treatment on the basis of a DBPCFC, which is a research tool that is not used in routine clinical practice. The diagnosis and management of peanut allergy in daily practice relies upon a clinical history (by which the clinician establishes the pre-test probability of the diagnosis), and then measuring allergen sensitization with SPT and/or IgE to arrive at a post-test probability of peanut allergy (Roberts and Lack, 2005; Sicherer and Wood, 2013). These assessments are therefore dependent on the predictive power of such tests to confirm the clinical history, and nomograms incorporating the likelihood ratio have been established based on observational studies. In clinical practice, if the post-test probability of peanut allergy remains uncertain because the combination of the test result and the clinical history are indeterminate, then a food challenge may be necessary as an additional procedure to definitively establish known allergy. However, eliciting a convincing history of a recent allergic reaction to peanut establishes a pre-test probability of > 90%, such that a positive test result of any kind effectively

clinches the diagnosis. This obviates the need for a risky food challenge procedure for confirmation, and is the way most food-allergic subjects are diagnosed in practice (Gupta et al, 2013). In addition, supportive clinical decision points (eg, a peanut IgE of ≥14 $kU_A/L$) for diagnosis have been derived from allergen-specific IgE cutoff levels that are 95% predictive (Sampson, 2001), and these decision points have been widely adopted clinically. The objective of the current study is to expand the AR101 safety experience by testing it in a placebo-controlled fashion in this clinical population, which may be more representative of the kinds of subjects likely to be offered therapy, as compared to those reacting at or before 100 mg of peanut protein in a screening DBPCFC conducted during a rigorously controlled pivotal trial.

## 1.4 Known and Potential Risks and Benefits of AR101

### 1.4.1 Risks

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

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 < l% 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 OIT that has been reported in the literature is EoE, affecting an estimated 3% 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 the 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.

### 1.4.2 Benefits

There is no guarantee that participation in this study will help the subject. Information from this study may help researchers to better understand peanut allergy or to develop future tests or treatments to help patients with this condition.

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

# 2. OBJECTIVES

## 2.1 Primary Objective

The primary objective is to assess the safety and tolerability of AR101 when used in a characterized oral desensitization immunotherapy (CODIT)™ regimen for approximately 6 months in peanut-allergic children.

## 2.2 Secondary Objectives

The secondary objectives are to characterize the frequency of all treatment-related AEs by study period, especially those of interest (defined in Section 7.3.4), and AR101's effect on asthma control and immune parameters.

# 3. STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled safety study of AR101 using the CODIT regimen in peanut-allergic children. Up to 500 peanut-allergic children ages 4 to 17 years will be randomized in a 2:1 ratio to AR101, a pharmaceutical-grade peanut allergen formulation, or placebo. The study will consist of a screening phase and a double-blind treatment phase that includes an initial 2-day escalation period and an up-dosing period. Subjects will be approached at the time of enrollment about donating saliva and additional blood samples to support exploratory biomarker analyses in a sub-study (Appendix 7). Participation in this sub-study is voluntary and requires signing separate consent and assent documents.

After completion of the up-dosing period, all study exit procedures, and treatment unblinding, subjects who received AR101 may participate in an open-label maintenance trial, known as Study ARC011; subjects who received placebo will be offered up-dosing and maintenance treatments with AR101 in Study ARC008. For subjects participating in follow-on studies, both follow-on protocols must be activated at the study site before subjects can complete all of the required ARC007 study exit procedures. Certain procedures (specifically, completion of questionnaires) and treatment unblinding will be completed at a later unscheduled visit if necessary to accommodate institutional review board (IRB) review of the follow-on protocols and shipment of open-label AR101. Additionally, all major data queries must be resolved before subjects complete exit procedures and proceed to a follow-on study. Subjects will remain on blinded study treatment and have an unscheduled visit every 4 weeks or sooner until all exit requirements are met.

The primary endpoint of the study is the frequency of TEAEs, including SAEs, during the overall study period. Secondary endpoints are frequency of premature discontinuation of dosing due to AEs; frequency of premature discontinuation of dosing due to chronic / recurrent GI AEs; proportion of chronic / recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing; frequency of allergic reaction (hypersensitivity) AEs occurring during up-dosing, normalized for duration of treatment; frequency of anaphylaxis as defined in the protocol; frequency of use of epinephrine as a rescue medication; frequency of accidental ingestions of peanut and other allergenic foods and severity of any resultant reactions; and assessment of asthma control using the Asthma Control Test (ACT) questionnaire and frequency of use of asthma rescue medication (short acting beta-agonists) in subjects with asthma.

Exploratory endpoints include changes in peanut- and peanut component-specific serum IgE and $IgG_4$ levels, changes in peanut SPT wheal diameter, changes in Total Nasal Symptom Score in subjects with allergic rhinitis, and changes in scores of the food allergy related quality of life questionnaire (FAQLQ) and food allergy independent measure (FAIM) questionnaire.

The Screening/Baseline Period is up to 21 days. Eligible subjects will be randomized in a 2:1 ratio to receive escalating doses of either AR101 or placebo, in 2 phases. Randomization will be stratified by age group (4 to 11 years and 12 to 17 years). Following a 2-day initial escalation phase, the up-dosing phase will be a minimum of 20 to a maximum of 40 weeks in duration in order to achieve the 300 mg/d dose level. Subjects reaching this dose of 300 mg/d will continue for an additional 2 weeks to ensure tolerability of the 300 mg/d dose. If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study. For subjects terminating early for GI AEs, additional observational follow-up will occur monthly in clinic or by phone for up to 6 months or until the symptoms have resolved or stabilized, or the Investigator deems them to be irreversible, according to details described further in Section 6.5.

Beginning at signed informed consent and assent as age-appropriate, all AEs 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 Exit or Early Discontinuation Visit, whichever comes first, with the exception of GI AEs, detailed further below. 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 may be required. Subjects who discontinue dosing prematurely due to chronic/recurrent GI AEs will complete the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS™ version 2.0) questionnaire and return to the clinic for evaluation monthly for at least 6 months (if the subject is asymptomatic, telephone follow-up with an Investigator may substitute for in-clinic visit, at the Investigator's discretion). If chronic/recurrent GI AEs persist beyond 6 months, subjects are to continue to be followed with monthly clinic visits (telephone follow-up with an Investigator may substitute for in-clinic visit, at the Investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management or the Investigator deems them to be irreversible. The protocol provides additional specific guidance about symptomatic medical management and referrals to a gastroenterologist, as necessary, in Section 7.3.4.2. Treatment will be administered in a double-blind fashion.

A DSMC has been established to monitor the study for safety.

### 3.1 Study Periods

The study consists of a screening period after which eligible subjects will proceed through 2 study periods, as tolerated:

- Initial Escalation
- Up-Dosing

## 3.2 Initial Escalation

All Initial Escalation doses will be administered by investigational site personnel to the subjects under direct supervision. Eligible subjects will be randomized and receive treatment with IP on Day 1, starting at a dose of 0.5 mg, increasing the dose at 20- to 30-minute intervals to a maximum dose of 6 mg (Table 1), according to the Schedule of Events (SOE) in Appendix 1. Subjects who fail to tolerate ≥ 3 mg dose on Day 1 will be considered escalation failures and will be discontinued. Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on the following day, Day 2. Subjects who do not tolerate this confirmatory dose will be discontinued. Subjects who tolerate this confirmatory dose will enter the Up-Dosing Period.

**Table 1: Initial Escalation Schedule**

| **Initial 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 |
| **Day 2 Dose Number** | **Investigational Product Dose, mg** | **Cumulative Dose, mg** |
| 1 | 3 | 3 |

[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 at least a single 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 and will be discontinued from the study.

## 3.3 Up-Dosing

Subjects will receive IP starting at a dose of 3 mg once daily and will gradually escalate every 2 weeks to a maximum of 300 mg once daily, according to the Up-Dosing Schedule (Table 2). All first escalation doses will be administered under direct observation in the 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 requirements for monitoring and emergency intervention are met by the facility). Subsequent doses will be dispensed to the parent/guardian and administered at home. Doses may be adjusted for tolerability or inter-current illness by the Investigator, except no down-dosing below 3 mg/day is allowed. The allowed dose levels are shown in Table 2. Up-dosing may thereby be extended to a maximum of 40 weeks in order to reach 300 mg and should not exceed this period.

Subjects unable to escalate to 300 mg within 40 weeks will be considered escalation failures. Subjects able to escalate to 300 mg will continue taking the 300 mg dose for an additional 2 weeks to ensure tolerability prior to exiting ARC007. If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study.

**Table 2: Up-Dosing Schedule**

| Up-Dosing Schedule | | | |
|---|---|---|---|
| **Dose Number** | **Investigational Product Dose, mg** | **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 | 2[b] | 25 |

[a] Interval includes Day 2 of Initial Escalation.

[b] If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study.

## 3.4 Treatment Unblinding and Rollover to Studies ARC011 and ARC008

The treatment assignment for each subject will be unblinded after all exit visit procedures are completed and all major data queries for the subject have been resolved. For subjects participating in follow-on studies, both follow-on protocols must be activated at the study site before subjects can complete all of the exit procedures.

Subjects who received AR101 and completed ARC007 will have the option to participate in the ARC011 study. The ARC011 study is an open-label safety extension study of ARC007 to evaluate the safety and tolerability of 300 mg/d maintenance dosing for up to 6 months. After completing Study ARC011, subjects will be able to proceed to ARC008 for further maintenance dosing.

Subjects who received active treatment but did not reach 300 mg/d within 40 weeks or were unable to tolerate 300 mg daily for 2 weeks by 48 weeks after Day 1 will not be eligible for enrollment in ARC011 or ARC008.

Subjects who received placebo and completed ARC007 will be offered up-dosing and maintenance treatment with AR101 in the ARC008 study. In ARC008, these subjects will

undergo an escalation schedule identical to that for active subjects in the ARC007 study and then continue on maintenance dosing at 300 mg/d.

All subjects who enter ARC008 will be allowed to continue receiving AR101 until it becomes commercially available or the development program is terminated.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible:

1. Age 4 to 17 years, inclusive
2. A history of physician-diagnosed IgE-mediated peanut allergy that includes the onset of characteristic allergic signs and symptoms within two hours of known oral exposure to peanut or a peanut-containing food. While IgE-mediated reactions have varied presentations, in general characteristic allergic signs and symptoms are objective and affect the target organs of the skin, GI tract, upper and/or lower respiratory tract, cardiovascular system, or a combination (Appendix 2)
3. Mean peanut wheal diameter on SPT of ≥ 8 mm greater than the negative saline control at Screening
4. Serum IgE to peanut of ≥ 14 $kU_A/L$ at Screening
5. Written informed consent from the subject's parent/guardian
6. Written assent from the subject as appropriate (eg, above the age of 7 years or the applicable age per local regulatory requirements)
7. Use of effective birth control method in sexually active females of childbearing potential

## 4.2 Exclusion Criteria

1. Subjects in whom the clinical diagnosis of peanut allergy is uncertain
2. History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension (see Section 5.10)
3. Use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers, or tricyclic antidepressants (see Section 5.10)
4. History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of screening
5. 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
6. History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema

7. Severe persistent asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] Criteria Steps 5 or 6, see Appendix 3)
8. Mild or moderate persistent asthma (2007 NHLBI Criteria Steps 1 to 4), if uncontrolled or difficult to control as defined by any of the following:
    a. 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
    b. Inhaled corticosteroid (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICSs based on NHLBI dosing chart); or
    c. One hospitalization in the past year prior to screening for asthma; or
    d. Emergency room (ER) visit for asthma within 6 months prior to screening
9. 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:
    a. History of daily steroid dosing for > 1 month during the past year; or
    b. 1 steroid course in the past 3 months; or
    c. > 2 steroid courses in the past year ≥ 1 week in duration
10. 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
11. Inability to discontinue antihistamines 5 half-lives before the screening SPT and initial day of escalation
12. Lack of an available palatable vehicle food to which the subject is not additionally allergic
13. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector
14. Use of omalizumab or any other monoclonal antibody therapy within the 6 months prior to screening or any current immunomodulatory therapy besides aeroallergen or venom immunotherapy or corticosteroids (see also Section 5.10)
15. Having received at least one dose of AR101 in a previous Aimmune or Allergen Research Corporation study
16. Use of other forms of peanut immunotherapy (eg, oral, sublingual, epicutaneous) within 6 months prior to screening
17. Participation in another clinical trial within 30 days or 5 half-lives of the IP, whichever is longer, prior to randomization
18. Concurrent administration of build-up phase of immunotherapy to another allergen (ie, subject has not reached maintenance dosing)
19. Pregnancy or lactation
20. Having the same place of residence as another subject in any AR101 study

## 4.3 Early Termination

### 4.3.1 Criteria for Early Termination

Any subject will be prematurely terminated from additional IP exposure for the following reasons:

1. Life-threatening symptoms (Consortium of Food Allergy Research [CoFAR] Grade 4; refer to the table in Appendix 5), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
2. Severe symptoms (CoFAR Grade 3; refer to the table in Appendix 5), including, but not limited to, those 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

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

1. Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma)
2. Starting any prohibited medication (Section 5.10), with no alternative medications available per the prescribing doctor, unless a waiver has been obtained from the Medical Monitor, as per Section 5.7
3. Pregnancy
4. Non-adherence (non-compliance) with IP 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 inter-current AEs) that require missed IP dosing for > 14 consecutive days, with the exception of the voluntary 30-day hiatus for GI-related AEs occurring at or before the 20-mg dose level

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

1. The subject elects to withdraw consent from all future study activities, including follow-up.
2. The subject is lost to follow-up (ie, no further follow-up is possible because attempts to reestablish contact with the subject have failed).
3. The subject develops biopsy-documented EoE.
4. 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.
5. The subject dies.
6. The Sponsor discontinues the study.

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

### 4.3.2 Follow-up of Subjects Who Discontinue Treatment

Subjects who prematurely discontinue treatment will be brought in for an Early Discontinuation Visit approximately 14 days after their last dose of 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 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), whichever comes first.

All subjects who discontinue treatment due wholly or in part to GI AEs will be instructed to complete the PEESS v2.0 questionnaire (Franciosi et al, 2011) monthly for 6 months. These subjects will also be asked to continue to fill out their daily diary for the same 6-month duration. Additional instructions for the follow-up of subjects who discontinue treatment due wholly or in part to GI AEs are provided in Section 7.3.4.2.

### 4.3.3 Subject Replacement

No subject who undergoes early discontinuation after receiving at least 1 dose of IP will be replaced.

## 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. The capsules used in this study will include the following strengths: 0.5, 1, 10, 20, and 100 mg each of peanut protein. AR101 is characterized by high performance liquid chromatography and by specific enzyme-linked immunosorbent assay (ELISA) for key allergenic proteins to demonstrate stability and lot-to-lot consistency. Placebos, containing only excipients that are color-matched to the peanut flour, will be provided as matching capsules, identical to the active capsules.

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

All IP (both peanut allergen and placebo) will be packaged and labeled at the central packaging facility. The products will then be shipped to a drug depot where they will be labeled and inventoried for shipment to the clinical sites. Investigational products will be shipped by the drug depot to the investigational site or the investigational site's pharmacy, according to site-specific institutional policies. Investigational product will then be distributed to each subject's parent/guardian by study site personnel. Investigational product will be dispensed to subjects on

the basis of matching randomization code to ensure dosing according to their assigned treatment arm and dose level, without the blind being broken for the subjects or the study personnel.

All 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 study drug for the duration of the study.

## 5.2 Preparation, Administration, and Dosage

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

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

Care must be taken not to inhale the powder as this could provoke worsening of asthma or induce an allergic reaction. 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 not consumed within 4 hours of mixing into a vehicle, the IP-vehicle food mixture should be discarded and a new dose mixed prior to consumption. If preparing a new dose is not feasible (eg, due to limited supply), the IP 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, this IP dose is to be discarded and the process restarted with a new IP dose. It is recommended that each dose of IP be taken at a consistent time (within a 4-hour period) each day that the dose is to be taken. A target interval of ≥ 8 hours should pass between doses. Per Investigator judgment, a home dose may be split into 2 portions for tolerability reasons, further discussed in Section 6.5.5.2.

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/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 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 (see Section 6.5.5), it is crucial that subjects take their dose according to their assigned schedule. No attempt should be made to make up for a missed dose if greater than 6 hours have elapsed since usual time of dosing.

## 5.3 Drug Accountability

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

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

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

## 5.4 Assessment of Compliance with Study Treatment and Monitoring

Daily dosing and any reaction to at-home dosing will be recorded in diary logs. 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 with the study diary.

The site will provide 24-hour emergency contact information.

## 5.5 Modification of Study Treatment

Investigational product doses may be adjusted by the study site Investigator if the subject is unable to tolerate their scheduled dose level. If such a dose modification occurs, the subject will return all unused capsules of IP during a dose adjustment visit, and be dispensed new 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, and SPT. Usual topical steroid use is permitted following SPT.

### 5.7 Prophylactic Medications

Although symptomatic treatments for chronic/recurrent AEs are permitted (eg, H-1 or H-2 histamine blockers, proton pump inhibitors, or beta-adrenergic agonists) such medications should, in general, not be routinely started in advance of symptoms; however, exceptions can be granted on a case-by-case basis following a mandatory discussion between the Investigator and the Medical Monitor. If started, the use of these medications should be minimized, and then discontinued, at the earliest medically appropriate opportunity.

### 5.8 Rescue Medications

Treatment of individual acute allergic reactions during ARC007 should be with either an antihistamine and/or epinephrine, along with IV fluids, beta-adrenergic agonist (eg, albuterol), oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely already to have an epinephrine auto-injector device, but for those who do not, an epinephrine auto-injector device will be provided. The expiry dates for the epinephrine auto-injectors should be tracked by the site and subject/families resupplied as necessary. Study staff must document in each subject's medical record that the subject and a 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 proceed with the symptomatic therapy in place.

### 5.10 Prohibited Medications

- Therapeutic immunomodulatory antibodies (commercially approved by a Regulatory Health Authority or experimental) last used within 6 months of screening
- Systemic corticosteroids used for any duration greater than 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
- Beta-blockers (oral)
- ACE inhibitors
- ARBs
- Calcium channel blockers
- 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;

however, if an Investigator deems use necessary, the use 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 a Medical Monitor.

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

# 6. STUDY PROCEDURES

## 6.1 Enrollment and Randomization

Following signed consent and assent (as appropriate), subjects will undergo screening procedures as outlined in Section 6.2. Eligible subjects will be randomized 2:1 to receive either AR101 or placebo and enter the Initial Escalation phase when they are in their state of baseline health and all comorbid medical conditions are stable. Randomization will be stratified by age group (4 to 11 years and 12 to 17 years of age) to ensure 2:1 randomization within the age groups. The stratified randomization will be performed using an interactive voice/web response system (IXRS).

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

## 6.2 Screening and Baseline

All screening procedures must be completed no later than 14 days from the signing of the informed consent and assent forms.

Screening will include the following assessments/procedures:

- Informed consent and assent, as age appropriate
- Inclusion/exclusion criteria review including obtaining and documenting medical records in source documents that support the history of reaction to known oral peanut exposure
- Medical, allergy, and dietary (food allergen exposure) history
- Completion of the FAQLQ and the FAIM questionnaire (prior to randomization)
- Asthma assessment by clinical history and ACT, for those subjects with a clinical history of asthma
- Concomitant medications
- Complete physical examination, including weight and height
- Vital signs (BP, pulse rate [PR], body temperature)

- Peak expiratory flow rate (PEFR) or spirometry ($FEV_1$)* (3 attempts are to be performed). Airflow assessment should as far as possible be measured at the same time at each visit.

  *Note: Only for children 6 years of age and above and able to adequately perform spirometry. 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. 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 Investigator's discretion. The attempt must be documented, and a clinical assessment is required.

- Serum pregnancy test for sexually active females of childbearing potential
- Blood draw to collect samples for:
  - Peanut-specific IgE, total IgE, and peanut-specific $IgG_4$ assays. The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
  - Complete blood cell count (CBC), obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Additional blood samples for optional exploratory immunologic studies. Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an additional volume of blood to be collected. Separate informed consent is required.
- Optional collection of saliva sample for exploratory biomarker development (separate informed consent required)
- SPT to peanut, saline, histamine, and perennial (eg, dog, cat, dust mite, cockroach) and seasonal pollen (eg, tree, grass, weed as per local practice) allergens
- Completion of the Total Nasal Symptom Score Sheet in subjects with allergic rhinitis
- AE monitoring
- Subjects will be instructed to continue to follow a peanut-avoidant diet for the duration of the study.
- Subjects and parents/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
  - Ensuring that the subject has an in-date epinephrine auto-injector and understands how and when to administer epinephrine
  - 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 will serve as the baseline measures for comparison to subsequent measures obtained during the course of the study.

## 6.3 Study Visits

### 6.3.1 Initial Escalation: Day 1

The Initial Escalation Day 1 visit should occur within 21 days of the signing of the informed consent and assent forms. Study eligibility will be confirmed prior to proceeding with randomization. Randomization through the IXRS will occur on Initial Escalation Day 1 prior to the first dose. 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 will be available at all times during the in-clinic dosing visits throughout the study. Subjects must be free from active wheezing or a flare of atopic disease (eg, atopic dermatitis), or suspected inter-current 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 to 7 days, depending on the Investigator-determined severity of the illness.

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

Day 1 visit in the CRC:

- Concomitant medication update
- Limited physical examination
- Diet (food allergen exposure) history update
- Pre-dose vital sign measurements (BP, PR, body temperature)
- PEFR (3 attempts are to be performed). Airflow assessment should be measured at approximately the same time for each visit.
- Administration of IP, with dosing beginning at 0.5 mg and progressing in graduated doses (if tolerated) of 1, 1.5, 3, and 6 mg. Following the first dose, subsequent doses will be delivered at 20- to 30-minute intervals. The schedule for initial day dose escalation is also shown in Table 1.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post-dose, and prior to next dose, and at 30-minute intervals thereafter, if the time between doses is extended, and for the duration of the post-dose observation period.
- Monitoring for AEs, including allergic symptoms (see below and Section 7.2)
- Completion of the Total Nasal Symptom Score Sheet in subjects with allergic rhinitis (Appendix 8)
- Peanut allergy teaching refresher (as per Section 6.2).

Subjects may drink fluids and eat foods to which they are not allergic 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 1.5 hours after completion of dose escalation, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the case report form (CRF) on the appropriate Dosing Symptom/AE form.

If Day 1 dose escalation is completed with no symptoms detected after 1.5 hours of post-dose observation, the subject will be able to leave the CRC. If the subject exhibited mild symptoms,

the duration of the observation period should be a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status, stage 3 anaphylaxis defined in Appendix 4, or who receives intensive therapy (to be determined by the Investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the Medical Monitor and discontinued from the study.

If dose-limiting symptoms occur at or before the 3 mg single dose, there will be no further dosing of IP, and the subject will be classified as an escalation failure and a non-responder for the purpose of primary and key secondary analyses. The subject will be asked to return to the CRC 14 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6). AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first.

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

### 6.3.2 Initial Escalation: 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 inter-current illness) creates a safety risk to provide the next dose, consistent with the rules for missed doses. 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 inter-current illness prior to continuing with Day 2 of the initial dose escalation.

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

Day 2 visit in the CRC:

- Concomitant medication update
- Limited physical examination
- Pre-dose vital sign measurement (BP, PR, body temperature)
- PEFR (3 attempts are to be performed). Airflow assessment should, as far as possible, be measured at the same time at each visit
- Oral administration of a single 3 mg dose of IP
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post-dose, prior to discharge, and as indicated per Investigator discretion during the post-dose

observation period. Subjects with moderate or severe symptoms should be monitored at least every 30 minutes, or more frequently as indicated.
- Monitoring for AEs, including allergic symptoms (Section 7.2).
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study
- Peanut allergy teaching refresher (as per Section 6.2)

At a minimum, subjects must be observed for 1.5 hours after dose administration, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom/AE form.

If Day 2 dosing is completed with no symptoms detected after 1.5 hours of post-dose observation, the subject will be able to leave the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be 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 4), or who receives intensive therapy (to be determined by the Investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the Medical Monitor and discontinued from the study.

If dose-limiting symptoms occur on Day 2, there will be no further dosing, and the subject will be classified as an escalation failure and a non-responder for the purpose of statistical analyses. The subject will be asked to return to the CRC 14 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6). AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, 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 (Study Day 3), and to continue daily home-dosing at that dose level for 2 weeks until next escalation.

On Day 3, the site is required to make telephone contact with the subject's parent/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 (Also Referred to as Build-up) Visits

Up-dosing will last from a minimum of 20 weeks to a maximum of 40 weeks and comprise 10 scheduled up-dosing visits (including the first 300 mg dose of the IP), with the potential for unscheduled visits for assessment of dose tolerability, dose reduction, dose re-escalation, or management of AEs. Subjects reaching this dose will continue in the study for an additional 2 weeks to ensure tolerability of the 300 mg/d dose. If the subject is unable to tolerate the 300 mg dose for the 2-week period, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study.

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 inter-current 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 inter-current 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.

Some or all of the following assessments/procedures will be completed during up-dosing visits in the CRC, according to the SOE:

- Return unused capsules to the clinic
- Monitoring for compliance
- Concomitant medication review
- Limited physical examination
- Diet (food allergen exposure) history update
- Pre-dose vital sign measurement (BP, PR, body temperature)
- PEFR (3 attempts are to be performed). Airflow assessment should as far as possible be measured at the same time at each visit.
- IP administration under observation in the clinic
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post-dose, prior to discharge, and at the Investigator's discretion during the post-dose observation period.
- Optional saliva collection at Week 6 Up-dosing Visit (Appendix 7)
- Monitoring for AEs, including allergic symptoms (Section 7.2)
- Completion of the Total Nasal Symptom Score Sheet in subjects with allergic rhinitis (Appendix 8)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.
- Take home capsules for daily dosing until next visit
- Peanut allergy teaching refresher (as per Section 6.2)
- Telephone follow-up call on the day after the visit

At a minimum, subjects must be observed for 1.5 hours after dose administration, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom/AE form.

If up-dosing is completed with no symptoms detected after 1.5 hours of post-dose observation, the subject will be able to leave the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status (stage 3 anaphylaxis defined in Appendix 4), 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's parent/guardian to inquire if any AEs (including allergic symptoms) occurred subsequent to the subject leaving the clinic, and to provide assistance in the recording of any such events in the diary.

A dose escalation attempt may be postponed 1 to 2 weeks if, in the clinical judgment of the Investigator, the current dose level has not been sufficiently well tolerated to proceed to the next dose level. Further, if an Investigator suspects that a subject has not tolerated, or is not tolerating, his or her current dose level, the Investigator should have the subject return to the clinic to determine whether a dose reduction is warranted, and if so, the magnitude of the reduction. Guidelines for setting the new, lower dose are outlined in Section 6.5.5 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 5.8. Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced ≥ 2 weeks apart, will result in the cessation of dosing and the subject being considered an escalation failure and non-responder. The subject will be asked to return to the CRC 14 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6) and is to be followed for safety in the interim.

### 6.3.4 Up-Dosing Interim (80 mg) Visit

The 80 mg in-clinic dosing visit is the approximate midpoint (approximately 10 weeks) of the Up-dosing Period. At this visit the following procedures are to be performed in addition to those performed at the other up-dosing visits (Section 6.3.3):

- Complete physical examination, including height and weight
- For subjects with a clinical history of asthma, asthma assessment by clinical history and ACT (Appendix 3)
- Urine pregnancy test for sexually active females of childbearing potential

### 6.3.5 End-Up-Dosing Phase Visit

The first 300 mg in-clinic dosing visit is the end of the Up-dosing Period. At this visit the following procedures are to be performed in addition to those performed at the up-dosing visits (Section 6.3.3):

- Complete physical examination, including height and weight
- For subjects with a clinical history of asthma, asthma assessment by clinical history and ACT (Appendix 3)
- Blood sample collection. Collect blood samples after measuring vital signs and PEFR and before administration of study treatment. These evaluations will serve as the exit visit screening/baseline values for the follow-on studies as applicable.
    - Peanut-specific IgE, total IgE, and peanut-specific $IgG_4$ (immunoglobulin assays).
    - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays
    - Optional blood samples. Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an addition volume of blood to be collected. Separate informed consent is required.
- SPT to peanut extract
- Optional saliva collection (Appendix 7)

### 6.3.6 Exit Visit/Early Discontinuation Visit

Subjects who tolerate their 300 mg dose for 2 weeks will have an Exit Visit per the SOE, and these evaluations will serve as the screening/baseline values for the follow-on studies as applicable. For subjects participating in follow-on studies, both follow-on protocols must be activated at the study site before subjects complete all of the required ARC007 study exit procedures. Certain procedures (specifically, completion of questionnaires and treatment unblinding) will be completed at a later unscheduled visit if necessary to accommodate IRB review of the follow-on protocols and shipment of open-label AR101. Additionally, all major data queries must be resolved before subjects complete exit procedures and proceed to a follow-on study. Blinded study treatment will continue to be dispensed to subjects until all exit requirements are met.

Subjects who fail initial escalation or up-dosing, or who prematurely discontinue treatment, will return to the site for an Early Discontinuation Visit that consists of the same procedures as the Exit Visit, except as noted below. An Early Discontinuation Visit is to occur 14 days after the last dose of IP. Subjects will return unused IP at this visit.

Subjects who withdraw from ARC007 wholly or in part due to intolerable GI symptoms, who are not enrolled in the optional saliva study, may be approached at the time of their Early Discontinuation Visit to provide voluntary consent to enroll and participate in the saliva sub-study. If this occurs, such subjects will provide a saliva sample as part of the Early Discontinuation Visit and then again during post-OIT follow-up (Appendix 7).

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

- Return unused capsules to the clinic
- Monitoring for compliance
- Concomitant medication review
- Complete physical examination, including weight and height
- Diet (food allergen) history
- Vital signs (BP, PR, body temperature)
- PEFR (3 attempts are to be performed). Airflow assessment should, as far as possible, be measured at the same time at each visit
- Urine pregnancy test for sexually active females of childbearing potential
- Optional saliva collection for those participating in the sub-study (at Early Discontinuation Visit only)
- Monitoring for AEs, including allergic symptoms (Section 7)
- Completion of the Total Nasal Symptom Score Sheet in subjects with allergic rhinitis
- Completion of the FAQLQ and the FAIM questionnaire after the completion of the exit procedures and unblinding
    - Treatment unblinding, FAQLQ, and FAIM will not be completed until both follow-on studies (ARC008 and ARC011) are activated at the study site, open-label AR101 is available, and all major queries are resolved. The subject will remain on blinded study treatment until all exit procedures are performed at a later unscheduled visit when all other conditions are met
- For subjects with a clinical history of asthma, asthma assessment by clinical history and ACT (Appendix 3)
- Blood draw (at Early Discontinuation Visit and for subjects whose exit procedures are completed > 6 weeks after the 300 mg visit only) to collect samples for:
    - Peanut-specific IgE, total IgE, and peanut-specific $IgG_4$ measurement (immunoglobulin assays)
    - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays
    - Optional blood draw. Note that these can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays. Separate informed consent is required.
- SPT to peanut extract

- Peanut allergy teaching refresher (as per Section 6.2)
- PEESS v2.0 questionnaire (at Early Discontinuation Visit only)
- Dispense capsules for daily dosing until next unscheduled visit (only for subjects who must continue double-blind treatment until all exit requirements are met)

## 6.4 Unscheduled Visits / Unscheduled Blood Draws

The procedures performed at unscheduled visits may include any or all of those performed at up-dosing visits as well as PEESS v2.0 questionnaire.

Subjects waiting for activation of follow-on protocols before completing their final exit visit procedures (treatment unblinding, FAQLQ, and FAIM) will continue blinded treatment and have an unscheduled visit every 4 weeks or sooner until all conditions are met for exiting the study. All exit visit procedures will be considered completed at the final unscheduled visit when unblinding, FAQLQ, and FAIM are completed. If the final unscheduled visit is more than 6 weeks after the scheduled exit visit, all exit visit procedures must be repeated. Additionally, laboratory evaluations must be repeated for subjects who exit the study > 6 weeks after the 300 mg visit, and these will serve as the screening/baseline values for the follow-on studies as applicable. Subjects will then enroll in the appropriate follow-on study based on their treatment assignment.

Additionally, if a subject or parent/guardian declares the intention to discontinue IP dosing, whether at a scheduled visit or an unscheduled visit, a blood draw should be performed to obtain a CBC, immunoglobulin assays, and optional blood and/or saliva samples (if the subject is participating in the sub-study). If a blood draw is performed at this time, it will take the place of the Exit Visit/Early Discontinuation Visit blood draw (Section 6.3.6).

## 6.5 Assessment and Treatment of Allergic Reactions to Peanut

### 6.5.1 Definitions of Symptom Severity

Subjects may develop allergic symptoms during the course of OIT, similar to those seen during other desensitization protocols (eg, venom immunotherapy, drug desensitization, desensitization to aeroallergens by subcutaneous injection). The severity of the reaction will be determined on the basis of the Investigator's judgment. The following definitions, developed to be consistent both with the PRACTALL (PRACTical issues in ALLergology Joint United States/European Union Initiative) consensus report and with the CoFAR grading system (table in Appendix 5) for allergic reactions, are provided as a general guide (Sampson et al, 2012).

**Mild symptoms**:

- Skin – limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema), or pruritus (mild, eg, causing occasional scratching)
- Respiratory – rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort
- Gastrointestinal – 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
- Gastrointestinal – 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
- Gastrointestinal – severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
- Neurological – change in mental status
- Circulatory – clinically significant hypotension

### 6.5.2 Assessment of the Tolerability of an Individual Dose of Investigational Product

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 3 illustrates the likely combinations of symptom severity and tolerability:

**Table 3: Allergy Symptom Severity and Investigational Product Dose Tolerability**

| Symptom Severity | Assessed Tolerability |
|---|---|
| None | Tolerated |
| Mild, oropharyngeal symptoms only | Tolerated |
| Mild, meeting pre-defined tolerability criteria (Section 6.5.1) | Tolerated |
| Mild, *not* meeting pre-defined tolerability criteria (Section 6.5.1) | Not tolerated |
| Moderate (except for rare exceptions, Section 6.5.1) | Not tolerated |
| Severe | Not tolerated |

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

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

**Mild symptoms**: When dosing with IP elicits an acute reaction characterized by the appearance of only a mild symptom or symptoms, the Investigator will be required to assess whether the

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

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

**Severe symptoms**: 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 6.5.3).

### 6.5.3 Assessment of the Tolerability of a Dose Level

#### 6.5.3.1 Assessment of Acute Symptoms Occurring After Dosing

The assessment of the tolerability of a single dose forms the foundation for assessing the tolerability of a dose level during home-dosing when acute symptoms arise in close temporal succession to dosing. With the report of moderate or severe symptoms occurring during home-dosing, the dose level should be considered to be not tolerated and the subject brought to

the clinic the day after the emergence of such symptoms for administration of the next dose of IP 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 at the time of the next scheduled dose.

The recurrence of a mild symptom or symptoms over the course of several days of home-dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated on the basis of the criteria listed above. If the investigational site is notified of mild dose-related symptoms on 4 or more occasions during a single week, the subject should be brought to the CRC for dosing under direct observation for assessment of the tolerability of the dose level. If mild dose-related symptoms are noted on 7 or more occasions during a 2-week dosing interval at a given dose level, that dose level should be considered not tolerated and appropriate action taken (Section 6.5.5).

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.

#### 6.5.3.2 Assessment of Chronic/Recurrent Symptoms

Gastrointestinal 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 6.5.6), 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 during up-dosing, at 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/d 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 6.6).

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 6.5.5.

### 6.5.4 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 1.
Investigator judgment will be required to determine the best course of action, with possible actions being the following:

- Extending the time interval between dosing (up to an additional 30 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 corticosteroids, as necessary, and discontinuing dose escalation
- Discontinuation of desensitization protocol

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

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

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

In general, if a subject requires only 1 dose 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 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 discontinue the initial escalation.

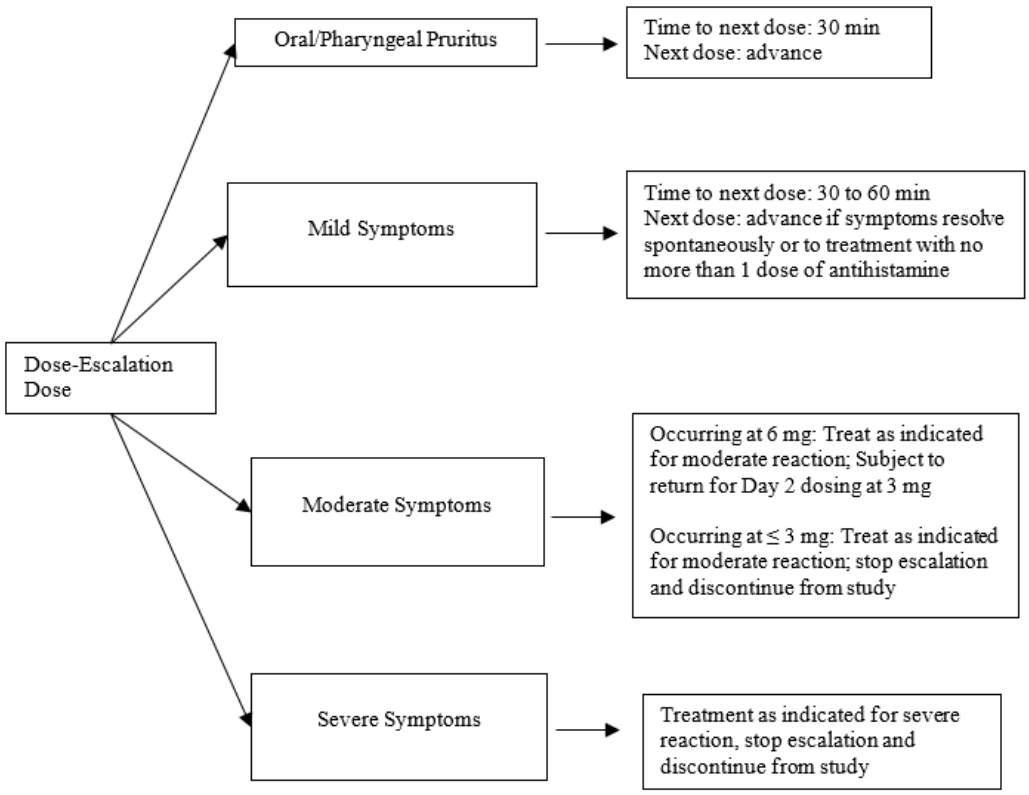
**Moderate symptoms**: For *moderate symptoms*, if the symptoms are not worsening or amassing at a rapid pace, then a stepwise approach to treatment may be taken at the discretion of the Investigator. If the first action undertaken is to implement an observation period, the observation period should 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 and the subject considered an escalation failure and desensitization non-responder. The decision to discontinue escalation is to be based solely on the determination of whether the allergic reaction was of moderate severity. Although it is generally the case that some form of treatment will be instituted for moderate symptoms, treatment is not a requirement for assessing an allergic reaction as being of moderate severity.

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

The Medical Monitor is available to answer any questions or to assist in any decisions related to the study protocol.

**Figure 1: Schematic for Initial Escalation Day 1**




### 6.5.5 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. Dosing must be at a dose level listed in Table 2; dosing below 3 mg/day is not allowed. The following possible actions are at the Investigator's disposal and are considered in greater detail in subsequent sections (Section 6.5.5.1, Section 6.5.5.2, and Figure 2):

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

action taken when a dose that has been observed in the CRC is assessed as not tolerated, if a dose elicits moderate or severe reactions that require no more than a single dose of epinephrine for treatment, 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 inter-current 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 inter-current 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 2 dose levels and maintaining the reduced dose level for at least 6 weeks – continuing dosing at a reduced dose level for at least 6 weeks prior to attempting re-escalation is mandatory if 2 doses of epinephrine are given to treat a single AE. In this case, discussion with the Medical Monitor is mandatory at 6 weeks, prior to the next up-dosing, to determine if dose escalation is warranted.
- 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.

#### 6.5.5.1 Reactions to In-clinic Dosing

If symptoms arise in the clinic after up-dosing, the Investigator is to determine whether or not the dose was tolerated (Section 6.5.3). The process algorithm for continued dosing after dose-related symptoms occur is described below and shown in Figure 2**.**

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

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

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). Dosing below 3 mg/day is not allowed. If the reduced dose is *assessed as tolerated*, the subject is to continue on that daily home dose for the ensuing 2 weeks. (See Section 6.5.5.2 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 and will be asked to return to the CRC 14 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6).

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 Investigator'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. (See Section 6.5.5.2 for actions to be taken in the event that symptoms develop during home-dosing.) If, following the first dose at a new dose level, the second dose at the new (increased) dose level is again accompanied by mild symptoms, but is *assessed as not tolerated*, the procedures outlined in the paragraph above should be followed.

If *moderate symptoms* occur with the first dose at a new dose level, except for rare instances, the dose will be *assessed as not tolerated*. The action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose under medical supervision. Dosing below 3 mg/day is not allowed. If this reduced dose elicits no allergic symptoms (ie, is well tolerated), the subject will continue on that daily home dose level for an additional 2 weeks. If the subject experiences mild symptoms at the reduced dose, the procedures for responding to a dose with mild symptoms should be followed (see above and Figure 2). If the subject experiences moderate symptoms at the reduced dose level, the subject should return to the CRC the next day and receive a further 1- or 2-step dose reduction (per Investigator judgment). If this reduced dose is well tolerated, it will be continued as the daily home dose for ≥ 2 weeks before re-escalation is attempted in the CRC. If the dose is not well tolerated, but elicits mild symptoms, then the treatment procedures for responding to mild symptoms should be followed (see above and Figure 2). If, however, the subject again experiences moderate symptoms at the reduced dose level, a discussion with the Medical Monitor is to ensue to reach a decision as to whether to continue the subject in the study.

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

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. Dosing below 3 mg/day is not allowed. 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 ≥ 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.

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

#### 6.5.5.2 Reactions to Dosing at Home

With the occurrence of symptoms of an acute reaction to IP after home-dosing, or any acute allergic reaction, parents/guardians are instructed to call the study site. The Investigator must then determine whether or not the dose was tolerated (Section 6.5.3). 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 2).

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

For home-doses *assessed as not tolerated* on the basis of acute dose-related symptoms, the same procedures described in Section 6.5.5, above, for adjusting up-dosing should be followed.

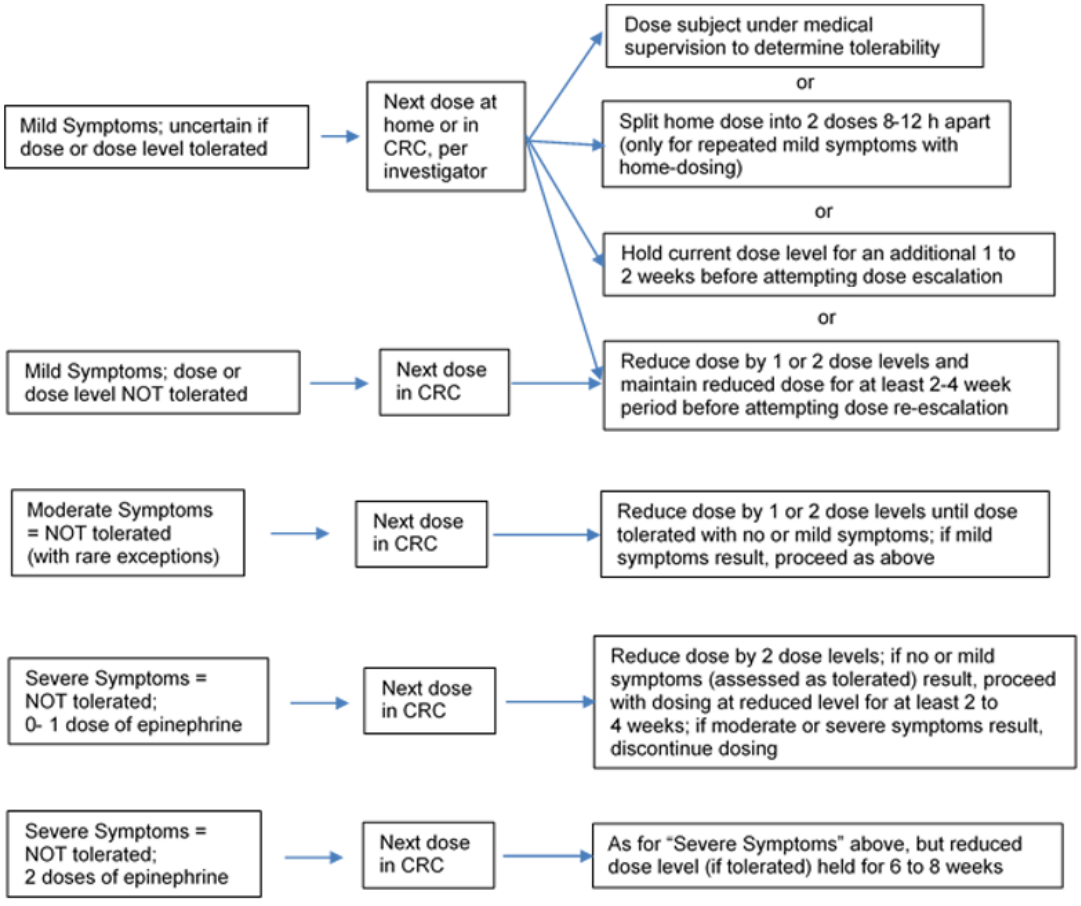
The recurrence of mild symptoms over the course of several days of home-dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated on the basis of the criteria listed above. In this circumstance, Investigator judgment will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

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

- Return to the CRC for dosing of a previously tolerated dose level, either a 1- or 2-step reduction (per Investigator judgment, based on severity of reaction). Dosing must be at a dose level listed in Table 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
- Discontinuation of dosing, with subsequent completion of an Early Discontinuation Visit

Any subject who discontinues up-dosing due to severe or repeated allergic reactions to IP should have their blood drawn for the assessment of peanut-specific immunoglobulin and CBC at, or as nearly as possible to, the time of the last dose but no later than at their Early Discontinuation Visit (Section 6.3.6). Additional assessments are to be performed per Early Discontinuation Visit schedule.

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



**Dose Adjustment in Response to Adverse Events**

At the Investigator 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 listed in Table 2) can be instituted as part of the treatment regimen for an inter-current AE. Dosing below 3 mg/day is not allowed. Also, if a pattern of decreased tolerability of IP during menses is discerned, then a temporary dose reduction can be instituted during this time. Temporary dose reductions for inter-current 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 may be resumed, with the biweekly escalation schedule kept unaltered.
- If a reduction in dose is maintained for 5 to 7 consecutive days, then the subject is to return to the CRC to undergo dosing under medical supervision. At the Investigator's discretion, the pre-reduction dose level may be resumed or dosing may continue at the reduced dose level. The biweekly escalation should be reset so that the subject receives ≥ 2 consecutive weeks of treatment at the dose level assigned (either the reduced or the pre-reduction dose level).
- If a reduction in dose is maintained for 8 to 14 consecutive days, then the next escalation attempted must be conducted in the clinic, and it should only be to 1 dose level above the reduced dose. If the escalation is successful, the subject should continue home-dosing for a minimum of 2 weeks, with his or her biweekly escalation schedule reset as necessary.

Doses of IP may also be withheld at the Investigator's discretion, in response to an inter-current AE. Doses withheld as part of the treatment for an AE constitute a special category of missed peanut OIT doses (Section 6.6).

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

Treatment of acute reactions should be with either an antihistamine and/or epinephrine, along with IV fluids, a beta-agonist (eg, albuterol, by inhaler or nebulizer), oxygen, and/or 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. If severe symptoms that qualify as Stage 3 anaphylaxis (defined in Appendix 4) occur at any time, dosing with IP will stop and the subject will be discontinued from the study as an escalation failure non-responder.

Antihistamines

If a subject receives antihistamines only, the dose escalation can be continued. 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 more than 2 doses of epinephrine will halt all further dosing of IP for the individual. The subject will be asked to return to the CRC 14 days following the last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6).

Epinephrine - Clinic

If a single administration of epinephrine is required during, or after, a dose escalation in the clinic, no further dosing of IP is to occur at that visit. The next dose of IP is to be reduced by 2 dose levels and administered in the CRC, but biweekly dose escalation should continue.

If a single administration of epinephrine is required a second consecutive time during, or after, 1 escalation attempt, the dose should be reduced by 2 dose levels, and the subject continued at that dose level for 6 to 8 weeks. After 6 to 8 weeks at the reduced dose, an escalation attempt may be tried in clinic.

If a single administration of epinephrine is required a third consecutive time during an escalation attempt, no further dosing should be attempted. Dosing in these subjects will be discontinued. They will be asked to return to the CRC 14 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6**)**.

Epinephrine - Home

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

## 6.6 Missed OIT (Investigational Product) Doses during Up-dosing

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

- Miss 1 to 2 doses in a row – The next dose would be at the current dose level and could be given at home

- Miss 3 to 4 doses in a row – The next dose would be the current dose and would be given under supervision in the CRC
- Miss 5 to 7 doses in a row – Initiate the next dose at approximately 50% of the last tolerated dose (to the nearest feasible available whole dose listed in Table 2 that is ≤ 50% of the last tolerated dose). Dosing below 3 mg/day is not allowed. 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 considered an escalation failure non-responder, and will be asked to return to the CRC 14 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6).
- Additionally, excessive missed dosing, defined as 3 consecutive days of missed doses on 3 or more occasions during the Up-dosing Period, for any reason other than treatment of an AE, constitutes an individual stopping rule and the subject is to stop, constitutes an individual stopping rule and the subject is to stop taking IP. The subject will be considered an escalation failure non-responder, and will be asked to return to the CRC 14 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6).
- Temporarily withholding IP dosing – this may be instituted as treatment for an inter-current 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.
- If IP has been withheld for 8 to 14 consecutive days as treatment for an AE or due to an IP dispensing error, dosing may be reinitiated at approximately 25% of the last tolerated dose (to the nearest feasible available whole dose listed in Table 2 that is ≤ 25% of the last tolerated dose). Dosing below 3 mg/day is not allowed. 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 6.5.3.2), the subject will be considered an escalation failure non-responder, and will be asked to return to the CRC 14 days following their last dose of IP to undergo an Early Discontinuation Visit (Section 6.3.6).

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

### 6.7 Skin Prick Test

Subjects will have SPTs performed using routine clinical procedures for food allergens (perennial allergens and seasonal allergens at screening only). After 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 extract of an allergen 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.

### 6.8 Visit Windows

Strict adherence to the dosing schedule should be maintained:

- Study visits should occur within a ± 2-day window of the scheduled visit date (ie, 2 days before or 2 days after the scheduled visit date)
- The Early Discontinuation Visit is to occur 14 days after the last dose of IP where IP dosing has been ceased for reasons other than study completion. The permissible window is minus 3 days to plus 7 days.

## 7. SAFETY MONITORING

This section defines the types of safety events 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 approximately quarterly throughout the study.

### 7.1 Reporting of Safety Events

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

- Any allergic symptoms observed during in-clinic dosing will be recorded directly on the Escalation/In-Clinic Dosing form (also referred to as an IP Administration form), and are not to be recorded on an AE form (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.
- If any safety event meets the definition of an SAE (whether or not related to dosing), it will also be recorded on an AE/SAE form.
- Non-serious adverse events of interest (AEIs) are reported on a non-serious AEI form and include anaphylaxis episodes meeting the criteria below, accidental food allergen exposures, GI AEs resulting in prolonged disruption of dosing, AEs associated with the use of epinephrine, and severe AEs (Section 7.3.4). These events will be reported to ProPharma Group following the same process as SAE reporting (with the exception of the requirement for regulatory submission). Only one form will be used per episode (eg, a systemic allergic reaction that meets anaphylaxis criteria in the protocol, involves

at least one severe symptom, and requires epinephrine use will be reported once, on either an SAE or non-serious AEI report form).

## 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 7.6.1).

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 AE eCRF. For each symptom, the AE eCRF will query "Is this an allergic reaction?" and the site should indicate yes/no accordingly.

## 7.3 Definitions

### 7.3.1 Adverse Event

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

### 7.3.2 Adverse Reaction

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

Adverse reaction is any AE caused by the drug.

### 7.3.3 Serious Adverse Event

An SAE is an AE that results in any of the following outcomes:

- Death
- 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.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of an SAE.

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 6.

### 7.3.4 Adverse Event of Interest

The safety profile of OIT is well established. The Phase 2 safety experience with AR101, as outlined in the Investigator Brochure, is generally consistent with this profile. Nonetheless, 5 types of AEs have particular importance in further assessment of the AR101 safety profile. These 5 types of AEs have been designated AEIs in ARC007: anaphylaxis events; GI AEs resulting in prolonged disruption of dosing; accidental food allergen exposure; AEs featuring a severe symptom; and AEs associated with the use of epinephrine. These events will be submitted to the pharmacovigilance team at ProPharma Group on a non-serious AEI form within 24 hours of site knowledge of the event. However, the Sponsor will not expedite reporting of AEIs to regulatory health authorities unless the event fulfills reportable criteria (Section 7.7.2).

It is possible that the same event could involve some combination of AEIs (eg, epinephrine use, anaphylaxis, severe symptoms) and/or seriousness criteria. Should this occur, one report form should be used so as to not duplicate reporting. The AEI form completion guidelines will be provided to sites in the manual of procedures.

The AEIs are each discussed further below.

#### 7.3.4.1 Anaphylaxis Event

An anaphylaxis event is an AE that meets the definition of anaphylaxis in the 2014 position paper by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines Group (Muraro 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 US Food and Drug Administration (FDA) Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies that states, “An adverse event or suspected adverse reaction is considered ‘life-threatening’ if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.” Thus, for the reporting of anaphylaxis as an SAE, the severity of the reaction, assessed according to the EAACI system for grading the severity of anaphylactic reactions (Muraro et al, 2007), is also to be taken into account. Guidelines for when anaphylaxis may fulfill the seriousness criterion as an important medical event are provided in Appendix 4.

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). These criteria were again affirmed in the recently published International consensus on (ICON) anaphylaxis (Simons et al., 2014).

#### 7.3.4.2 Gastrointestinal AE Resulting in Prolonged Disruption of Dosing (GI AEIs)

Gastrointestinal AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered 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
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus
- Any subject who permanently discontinues dosing who had experienced GI AEs (Section 4.3.1).

All subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent/ guardian, as appropriate, every month for 6 months. However, 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 for all subjects (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 will be asked to return to the clinic for evaluation monthly for ≥ 6 months (if the subject is asymptomatic, telephone follow-up with the Investigator may substitute for in-clinic visit, at the Investigator's discretion). If chronic/recurrent GI AEs persist beyond 6 months, subjects are to be followed with monthly clinic visits (telephone follow-up with an Investigator may substitute for in-clinic visit, at the Investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management.

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

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

#### 7.3.4.3 Accidental Food Allergen Exposure

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 7.3.3), in which case the AE 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.

#### 7.3.4.4 Adverse Event Featuring a Severe Symptom

The severity of symptoms will be determined on the basis of the Investigator's judgment. Severity definitions for allergic reactions to IP were developed to be consistent both with the PRACTALL consensus report and with the CoFAR grading system and are provided in Section 6.5.1 and the table in Appendix 5 as a general guide. Severe allergic AEs may include:

- 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.

Severity of other AEs will be assigned using other grading systems as discussed in Section 7.4.

#### 7.3.4.5 Adverse Events Associated with Use of Epinephrine

AEs may result in epinephrine use. Upon awareness of such an event, site staff will report it within 24 hours using the AEI form, independent of severity or relatedness, or whether it was administered 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.

### 7.4 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 grading of allergic reactions will be according to the definitions developed by the CoFAR group (Appendix 5).
- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 4).
- For grading the severity of all other AEs, the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) system will be used. The purpose of using the NCI-CTCAE system is to provide standard language to describe AEs (toxicities) and to facilitate tabulation and analysis of the data and for assessment of the clinical significance of treatment-related toxicities. The NCI-CTCAE provides a term and a grade that closely describes the AE. Each participating site will receive copies of the grading scales and event descriptions.

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 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.

### 7.4.1 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.

## 7.5 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 periodically to review accruing safety data. The committee will consist of individuals with extensive multicenter 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 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. AEs 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 Exit or Early Discontinuation Visit, whichever comes first. AEs 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 may be required. For the specific case of GI-related AEIs, the need for additional follow-up is outlined in Section 7.3.4.2. 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)

### 7.6.1 Recording and Reporting Procedures

A multi-screen AE eCRF will be used allowing all AEs to be submitted through a single reporting mechanism (Figure 3). Serious AEs will require additional information reported on additional screens within the EDC system. Source documents, with subject identifiers redacted, can be scanned and attached to the AE form as well. The Investigator will treat subjects experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

### 7.6.2 Serious Adverse Event Recording and Reporting Procedures

Serious AEs 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:

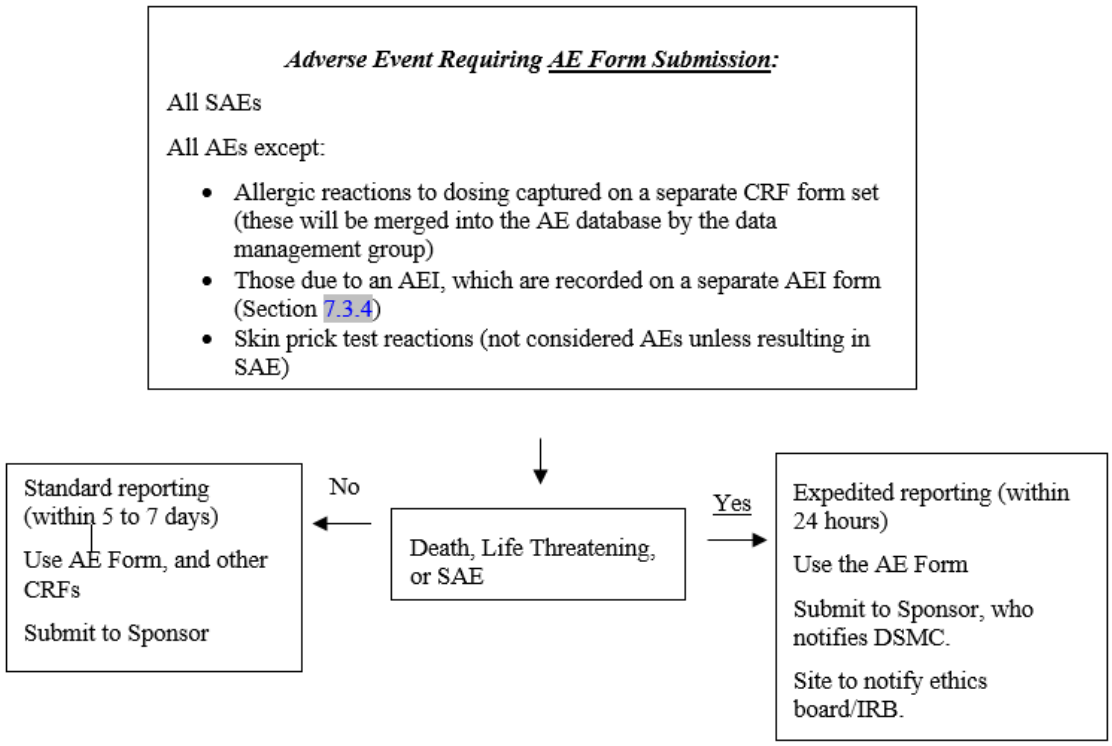
- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to test article
- Action taken

The Investigator will apply his/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, IRB / EC, or the Sponsor may suspend further trial treatment or procedures at a site. The study Sponsor and the regulatory health authorities retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

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

**Figure 3: Reporting Decisions for Adverse Events**




1. Site to notify the site's Principal Investigator of event(s)
2. Site to 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. 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.
4. In the event of a death, the AE Form must be completed and transmitted along with other supporting data (death certificate, medical notes, etc).

## 7.7 Serious Adverse Event Notification

### 7.7.1 Notifying the Sponsor

Investigators will provide the Reporting Center (ProPharma Group, St. Paul, MN) with data of all SAEs as defined per the protocol on an ongoing basis. As noted above, the initial contact should be within 24 hours of site awareness of the event.

### 7.7.2 Expedited SAEs Reporting to Regulatory Health Authorities

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

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

### 7.7.3 Notifying the DSMC

The Reporting Center 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 IRBs/ECs if requested.

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

- An ER visit;
- Hospitalization;
- More than 2 doses of epinephrine being given as treatment for the same episode;
- Assessment of the anaphylaxis as severe, as defined in Appendix 4.

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

### 7.7.4 Notifying the Institutional Review Board and Ethics Committee

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

## 7.8 Other Safety Assessments and Precautions

### 7.8.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in Appendix 1. Height and weight will also be recorded at specified visits. Vital signs will be measured, including BP, PR, and body temperature. Except where a complete, age-appropriate physical examination is specifically indicated, a limited physical exam may be performed.

### 7.8.2 Prior and Concomitant Medications

Prior and concomitant medications will be documented in the CRF.

### 7.8.3 Pregnancy Testing and Contraception

#### 7.8.3.1 Pregnancy Testing

All sexually active female subjects of childbearing potential will undergo a serum pregnancy test at screening and then urine pregnancy tests at specific subsequent visits.

#### 7.8.3.2 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. Oral immunotherapy, 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, sexually active female subjects of childbearing potential are required to practice effective birth control for the duration of the study.

Sexually active female subjects are to use either:

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

## 7.9 Stopping Rules

### 7.9.1 Overall Stopping Rules

The study will be suspended at any time if a treatment-associated death occurs in a subject receiving AR101 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 AR101. Suspension of the study will entail halting the enrollment of subjects and refraining from any dose increases, but will not entail cessation of dosing unless so directed by the FDA, the applicable regulatory health authority(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 continually 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.

### 7.9.2 Individual Stopping Rules

Individuals may stop the study at any time by withdrawing their consent if they experience subjectively intolerable AEs, dosing symptoms, or for any other reason. In addition, > 7 consecutive days of missed daily 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. During Up-dosing, subjects must halt up-dosing and re-start with a reduced dose if more than 4 days of dosing are missed. Missing 3 or more consecutive days on 3 occasions is an individual stopping rule, as is missing 15 or more consecutive days of dosing for any reason, with one exception of the voluntary 4-week hiatus for GI AEIs occurring at or before the 20 mg dose, as specified in Section 6.5.3.2.

Occurrence of any of the following will result in the cessation of dosing and the subject being discontinued from the study as an escalation failure non-responder, resulting in an Early Discontinuation Visit within 14 days:

- Failure to accomplish up-dosing of IP after 3 attempts
- Failure to identify a tolerated dose of IP after 3 attempts at dose reduction

Finally, administration of 3 or more doses of epinephrine for the treatment of any dose-related allergic reaction in any subject is an individual stopping rule.

## 8. OPTIONAL MECHANISTIC SUBSTUDIES

Subjects in ARC007 are eligible to participate in the optional collection of saliva and peripheral blood specimens for future studies designed to better understand the biological basis and treatment of food allergy. The provision of these additional specimens is voluntary and does not affect the subject's participation in ARC007. The parents/guardian and subject, as appropriate, will be asked to sign separate informed consent and assent forms to participate in this sub-study. The additional tubes of peripheral blood are to be collected at the same time points as the routine laboratory work in ARC007 and do not require additional visits or phlebotomy. The saliva specimens will be collected as part of an ongoing collaboration with researchers at Cincinnati Children's Hospital Medical Center to analyze the salivary mRNA transcriptome of participants receiving OIT, as outlined further in Appendix 7.

## 9. STATISTICAL CONSIDERATIONS

This protocol outlines the major statistical considerations for the ARC007 study. Full details on the statistical methodology to be used in the analysis and data handling for this trial will be described in the statistical analysis plan (SAP) to be developed prior to database lock and statistical analysis.

Data will be summarized using descriptive statistics within treatment group. No specific hypothesis testing or comparisons between the treatment groups are planned for this study.

Details of within-group comparisons relative to baseline values and any exploratory comparisons between groups will be described in the SAP.

Descriptive statistics will be presented in the following manner:

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

Data will be summarized by treatment group and treatment phase.

Data will be summarized in tables for each treatment group, treatment groups combined, and treatment phase.

Data will be listed for each subject.

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

## 9.1 Analysis Populations

The primary population of analysis for all analyses will be the safety population. The Safety population will consist of all subjects who receive study treatment during ARC007.

A per-protocol population, limited to subjects who have no major protocol deviations and who undergo Exit Visit procedures, may be defined. Exclusions will be determined by data review and documented before database lock.

Additional analysis populations may be defined in the SAP.

## 9.2 Study Endpoints

### 9.2.1 Primary Endpoint

The primary endpoint is the frequency of TEAEs, including SAEs, during the overall study period.

### 9.2.2 Secondary Endpoints

- Frequency of premature discontinuation of dosing due to AEs
- Frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs
- Proportion of chronic/recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing
- Frequency of allergic reaction (hypersensitivity) AEs occurring during up-dosing, normalized for duration of treatment
- Frequency of anaphylaxis as defined in the protocol
- Frequency of use of epinephrine as a rescue medication
- Frequency of accidental ingestion of peanut and other allergenic foods and severity of any resultant reactions

- Assessment of asthma control using the ACT questionnaire and frequency of use of asthma rescue medication (short acting beta-agonists) in subjects with asthma

#### 9.2.3 Exploratory Endpoints

- Changes in peanut-specific and peanut component-specific serum IgE and IgG4 levels
- Changes in peanut SPT mean wheal diameter
- Changes in Total Nasal Symptom Score in subjects with allergic rhinitis
- Changes in scores of FAQLQ and the FAIM questionnaire

### 9.3 Subject and Demographic Data

#### 9.3.1 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic data will be provided for all enrolled subjects. Baseline characteristics (body weight and height) and demographic data (age, race, and sex) will be collected.

Statistical presentation for baseline and demographic characteristics may be further summarized by baseline peanut-specific serum IgE.

#### 9.3.2 Use of Medications

All medications used will be coded using the WHO Drug Dictionary. The number and percentage of subjects receiving concomitant medications or therapies will be summarized descriptively.

#### 9.3.3 Study Disposition

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

#### 9.3.4 Adverse Events

Adverse events will be coded on the basis of the Medical Dictionary for Regulatory Authorities terminology. Events will be tabulated by system organ classification and preferred term. Selected summaries will also be prepared by severity and relationship to study treatment.

### 9.4 Sample Size and Power Calculations

ARC007 is a safety study that will add critical placebo-controlled observations to the ongoing safety database of AR101. As such, there are no efficacy endpoints in the study, no specific efficacy-related hypotheses to be tested, and no prospective sample size calculations performed related to the power to detect a pre-specified treatment effect size.

A sample size of up to 500 subjects, randomized in a 2:1 ratio to AR101 or placebo, along with subjects enrolled in other studies in the clinical program will provide a sufficient number of subjects to fulfill the regulatory requirement for data on at least 600 subjects dosed for 6 months at 300 mg/d.

### 9.5 Web-Based Data Collection and Management System

Data collection will occur via an EDC system to allow easy access to enrollment 24 hours/day, 7 days/week. Upon enrollment, a form submission schedule is generated for each subject by study visit that permits direct access to each electronic CRF for data entry. As data are entered, they are validated through range and within-form consistency checks. The Investigator will be required to ensure that all CRFs are completed in a timely fashion for all subjects at their site.

### 9.6 Certification in the Use of Electronic Data Entry System

The clinic and laboratory staff will be trained in the use of the EDC 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.

### 9.7 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.

### 9.8 Access to Data

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

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

### 10.1 Statement of Compliance

This study will be conducted using current Good Clinical Practice (GCP), as delineated in the 21 CFR Parts 50, 54, 56, and 312 and in the ICH E6, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents (informed consent form and assent forms) will be reviewed and approved by an appropriate IRB(s)/EC(s) as well as FDA and other applicable regulatory health authority(ies). Any amendments to the protocol will also be approved by the Sponsor, IRBs/ECs, and submitted to the applicable health authorities before they are implemented. Any amendments to the consent materials must also be approved by the Sponsor and IRB(s)/EC(s) before they are implemented.

### 10.2 Informed Consent and Assent

The informed consent form (ICF) is a means of providing information about the study to the parent/guardian of a prospective subject and allows for an informed decision about participation in the study. Because the study population will be comprised of children, parents or legal guardians will be asked to read, sign, and date an ICF before a child enters the study, takes IP, or undergoes any study-specific procedures. Children will sign an assent form, as required by the IRB/EC. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The ICF and assent form will be reviewed to determine whether a revision is required whenever the protocol is amended, or new safety information becomes available. A copy of the ICF will be given to a prospective parent/guardian for review. The Investigator or designee, in the presence of a witness, will review the ICF and answer questions, as well as emphasize the need to avoid allergen exposure other than to IP, and the importance and necessity to continue exposure to IP to induce desensitization. The prospective subject (as age appropriate) and subject's parent/guardian will be told that being in the study is voluntary and that he or she may withdraw, or withdraw his/her child, from the study at any time, for any reason.

### 10.3 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 to the Sponsor.

## 11. RESOURCE SHARING

All data derived from this study are the sole property of the Sponsor and will be sent to the Sponsor or designee for storage and analysis. Subject data will be anonymized to maintain subject confidentiality. All data sets will be archived by the Sponsor or designee and may be made available to study investigators as well as interested, outside investigators with approval by the Sponsor.

The Sponsor will require the review and provide approval where appropriate of any abstracts or manuscripts prepared from these data prior to their submission for publication.

## 12. PROTOCOL DEVIATIONS

The Investigators and site staff will conduct the study in accordance with the protocol, GCP, and the site’s local and country specific regulatory requirements. Any departure from the study design or procedures constitutes a protocol deviation.

A major protocol deviation is a protocol deviation that may affect subjects’ rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data.

A non-major protocol deviation is a protocol deviation that does not have a major impact on subjects’ rights, safety, or well-being, or the completeness, accuracy, and reliability of the study data.

## 12.1 Reporting and Managing Protocol Deviations

The site's Principal Investigator has the responsibility to identify, document, and report protocol deviations. Protocol deviations may also be identified during site monitoring visits or other reviews of study conduct. All protocol deviations will be reported in the clinical database.

The Sponsor's Medical Monitor (or designee) has the responsibility to review all protocol deviations periodically and to classify them as major or non-major. All major protocol deviations require additional documentation as directed by the Sponsor.

Whenever applicable, corrective and preventive actions will be developed by the site and approved by the Sponsor, or developed by the Sponsor and communicated to the site(s) and implemented promptly.

## 13. REFERENCE LIST

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## Appendix 1: Schedule of Events for ARC007

| Visit | | Screening/ Baseline | Initial Escalation | | Up-dosing Period | | | Exit Visit | Early Discontinuation Visit[b] | Unscheduled Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day 1 | Day 2 | CRC Dosing | Interim (80 mg) Visit | 300 mg Visit | | | |
| **Timing** | | **Day 1 within 21 days after Consent/Assent** | | | **~Every 2 weeks for 20 to 40 weeks** | **Approximately Week 10** | **≤ Week 40[a]** | **14 days after 300 mg Visit[c]** | **14 days after last IP dose** | **As needed** |
| Informed consent & assent | | X | | | | | | | | |
| Inclusion & exclusion criteria | | X | | | | | | | | |
| Medical & allergy history | | X | | | | | | | | |
| Diet (food allergen) history | | X | X | | X | X | X | X | X | X |
| Concomitant medications | | X | X | X | X | X | X | X | X | X |
| Physical exam[d] | | X | X | X | X | X | X | X | X | X |
| Vital signs (BP, PR, temp) | | X | X[e] | X[e] | X | X | X | X | X | X |
| PEFR[f] | | X[g] | X | X | X | X | X | X | X | X |
| Pregnancy test[h] | | Serum | | | | Urine | | Urine | Urine | Urine |
| **Blood draw** | Total IgE & peanut-specific immunoglobulins | X | | | | | X[i] | | X | X[j] |
| | CBC | X | | | | | X[i] | | X | X[j] |
| | Optional blood sample(s)[k] | X | | | | | X[i] | | X | X[j] |
| Saliva collection, optional[k] | | X | | | X | | X | | X[l] | X |
| Skin prick test (food). Perennial, seasonal allergens at screening only | | X | | | | | X | X | X | X |
| ACT | | X | | | | X | X | X | X | X |
| Peanut allergy teaching | | X | X | X | X | X | X | X | X | X |
| FAQLQ & FAIM questionnaire | | X | | | | | | X[c] | X | X[c] |
| Total Nasal Symptom Score[m] | | X | X | | X | X | X | X | X | X |
| Monitor AEs/allergic symptoms | | X | X | X | X | X | X | X | X | X |
| Randomization in IXRS | | | X | | | | | | | |
| Administration of IP at site | | | X | X | X | X | X | | | X |
| Dispense/return unused IP | | | | X | X | X | X | X | X | X |
| Telephone follow-up[n] | | | | X | X | X | X | | | X |
| Monitor for compliance | | | | | X | X | X | X | X | X |
| PEESS v2.0 questionnaire[o] | | | | | | | | | X | X |

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BP = blood pressure; CBC = complete blood cell count; CODIT = characterized oral desensitization immunotherapy; CRC = clinical research center; FAIM = food allergy independent measure (questionnaire); FAQLQ = food allergy related quality of life questionnaire; $FEV_1$ = forced expiratory volume in 1 second; IP = investigational product; GI = gastrointestinal; IXRS = interactive voice/web response system; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PEFR = peak expiratory flow rate; PR = pulse rate; temp = body temperature.

a) If the subject is unable to tolerate the 300 mg dose for the 2-week period after the End Up-dosing (300 mg) Visit, dosing may continue up to a maximum of 48 weeks after Day 1 to ensure tolerability prior to exiting the study.
b) Subjects who discontinue dosing prematurely due to chronic/recurrent GI AEs will be asked to return to the clinic for evaluation monthly for ≥ 6 months after this visit. If the subject is asymptomatic, telephone follow-up with the Investigator may substitute for in-clinic visit, at the Investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will be followed with monthly clinic visits until the symptoms have resolved or are assessed to have stabilized with optimal medical management.
c) Any of the procedures below may be performed. Subjects waiting for activation of follow-on protocols before completing their final exit visit procedures will continue blinded treatment and have an unscheduled visit every 4 weeks or sooner until all conditions are met for exiting the study. All exit visit procedures will be considered completed at the final unscheduled visit when unblinding, FAQLQ, and FAIM are completed. If the final unscheduled visit is more than 6 weeks after the scheduled exit visit, all exit visit procedures must be repeated. Additionally, laboratory evaluations must be repeated for subjects who exit the study > 6 weeks after the 300 mg visit, and these will serve as the baseline evaluations for the follow-on studies. Subjects will then enroll in the appropriate follow-on study based on their treatment assignment.
d) A complete physical exam (including height and weight) is required at the Screening/Baseline, the 80 mg and 300 mg up-dosing visits, Exit, and Early Discontinuation visits. At the Investigator's discretion, a limited physical exam may be completed at other visits.
e) BP, PR, and body temperature; BP and PR within 15 to 30 minutes post-dose, prior to the next dose, and at 30-minute intervals thereafter, if the time between doses is extended, and for the duration of the post-dose observation period.
f) 3 attempts made with the best value recorded, measured at the same time at each visit
g) Peak expiratory flow rate (PEFR) or spirometry (FEV1) may be performed at the Baseline/Screening Visit
h) For sexually active females of childbearing potential only
i) Collect blood samples after measuring vital signs and PEFR and before administration of study treatment
j) Collect blood samples after measuring vital signs and PEFR and before administration of study treatment if the unscheduled visit is > 6 weeks after the 300 mg visit and is the final unscheduled visit when unblinding, FAQLQ, and FAIM are completed
k) For subjects for whom additional consent and assent have been provided only
l) For subjects who terminate dosing and enter observational follow-up, the final sample will be collected six months after study withdrawal or as close as practicable.
m) In subjects with allergic rhinitis only
n) On the day after the visit
o) To be performed every month for six months for subjects (1) for whom dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level, (2) who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus, or (3) who permanently discontinues dosing who had experienced GI AEs

## Appendix 2: Systems and Examples of Symptoms Involved in Acute IgE-mediated Reactions to Foods (Sampson et al, 2014)

Cutaneous
- Pruritus
- Erythema/flushing
- Urticaria
- Angioedema
- Contact urticaria

Ocular
- Pruritus
- Tearing
- Conjunctival injection
- Periorbital edema

Respiratory tract

Upper
- Pruritus
- Nasal congestion
- Rhinorrhea
- Sneezing
- Hoarseness
- Laryngeal edema

Lower
- Cough
- Wheezing
- Dyspnea
- Chest tightness/pain

Gastrointestinal
- Oral pruritus
- Oral angioedema (lips, tongue, or palate)
- Colicky abdominal pain
- Nausea
- Emesis
- Diarrhea

Cardiovascular
- Tachycardia
- Dizziness
- Hypotension
- Loss of consciousness/fainting

Miscellaneous
- Sense of impending doom
- Uterine cramping/contractions

## Appendix 3: 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 | Nighttime Awakenings | Lung Function | Interference with Normal Activity | Short Acting 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* | 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 |

*Normal $FEV_1$/FVC: 8-19 years of age = 85%; 20-39 years of age = 80%

## Appendix 4: 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 is fulfilled:

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

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

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

### Criteria for Anaphylaxis Severity Grading

| 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 |

Criteria for diagnosis and for severity grading adapted from Muraro et al, 2007, and Muraro et al, 2014.

## Appendix 5: Allergic Reaction Severity Grading

The CoFAR grading system for allergic reactions is displayed in the table.

### CoFAR Specific Grading System for Allergic Reactions

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

## Appendix 6: Guidance for Determining When an Episode of Anaphylaxis Should Be Reported as a Serious Adverse Event

For an episode of anaphylaxis to be considered an SAE, the Sponsor advises that the event satisfies one of the outcome-based definitions of SAE specified in Section 7.3.3 of the protocol, with the stipulations (denoted in *italics*) indicated. These stipulations follow from, and are consistent with, the criteria for DSMC reporting (Section 7.6.2):

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 4 and of a Grade 4 allergic reaction, as defined in the table in Appendix 5.*
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 an SAE:
    - *In general, for an anaphylactic episode to be classified as an SAE on the basis of being an important medical event, it should have resulted in an ER visit, and the ER visit should have been associated with intensive therapy. What constitutes intensive therapy is to be determined by the Investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit.*
    - *One or 2 intramuscular injections of epinephrine should ordinarily not be construed as intensive therapy.*
    - *If an Investigator assesses an episode of anaphylaxis to be an important medical event when the episode was of mild or moderate severity and did not require intensive therapy, the rationale for the assessment must be explained in detail in the narrative of the event.*

## Appendix 7: Exploratory Biochemical and Molecular Sub-study of Peanut-Allergic Children with Oral Immunotherapy-Related Gastrointestinal Symptoms

### Background

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

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

In OIT studies, GI AEs are typically prominent (Anagnostou et al, 2014; Yu et al, 2012; Blumchen et al, 2010; Jones et al, 2009) and account for a substantial proportion of premature discontinuations of study treatment (Burks et al, 2012; Varshney et al, 2011; Jones et al, 2009; Vickery et al, 2011). This was also observed in the completed ARC001 study and the ongoing ARC002 study. In the ARC001 study, 6 out of 29 subjects (21%) receiving active treatment discontinued prematurely. Four of the early discontinuations were attributed by the Principal Investigators to have been the consequence of recurrent GI AEs; and in 1 of these cases the diagnosis of EoE was subsequently established by endoscopic biopsy. In the other 2 discontinuations, ≥ 1 GI AE had occurred in each subject. In the ongoing ARC002 study, an open-label follow-on to the ARC001 study, 3 of the 4 subjects discontinued due to GI adverse events (nausea, vomiting, abdominal pain) during up-dosing in part 1, and 1 subject from group 2 discontinued due to a GI adverse event (dysphagia) during the low-dose maintenance period.

Repeated bouts of abdominal pain and vomiting are common to both EoE and chronic/recurrent OIT-related GI symptoms, suggesting a common, or at least a similar, etiology in at least a proportion of subjects. To date, ≥ 20 occurrences of OIT-related GI AEs have been confirmed histopathologically to be EoE as reported in the medical literature (Lucendo et al, 2014), and in still other cases the symptomatology and clinical course (with or without concomitant blood eosinophilia) have been highly suggestive of EoE (Narisety et at, 2009; Vickery et al, 2011). A recent review of the literature (Lucendo et al, 2014) has indicated that the incidence of confirmed EoE in OIT is on the order of 3% (ranging from approximately 1% to 5%).

Establishing the association between OIT and the subsequent development of EoE is not always straight forward. The time to onset of EoE during the course of OIT may vary depending on the allergen and OIT regimen. Many (Wasserman et al, 2011), though not all (Hofmann et al, 2009), of the reported cases of EoE with peanut OIT had developed GI symptoms early in the course of oral desensitization, whereas with milk OIT the occurrence of EoE has tended to be after reintroduction of milk into the diet (Sánchez-García, 2012; Maggadottir et al, 2014). Not all EoE occurring during OIT is necessarily caused by the OIT, however. Food allergies often occur to more than 1 type of food and allergies to foods often coexist with allergies to airborne and contact allergens.

Chronic GI AEs affecting participants in ARC007 have been designated as AEIs in the ARC007 protocol. The goal of the current sub-study is to explore the biology of these GI AEIs occurring during this trial using a readily available and noninvasive sampling method (saliva) in an attempt to overcome some of the difficulties in assessing intolerable GI AEs in subjects undergoing OIT.

**Rationale for the Proposed Study**

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

Specifically, this sub-study of ARC007 will enroll all willing subjects at screening, prior to dosing, and then collect further information from those subjects who go on to experience GI side effects during OIT and those subjects who do not (controls). To overcome the obstacles limiting traditional EoE evaluations in this context (eg, performance of an esophagogastroduodenoscopy [EGD]), an easily collected bio-specimen will be analyzed to determine whether patterns can be detected that correlate with patterns seen in other subjects with known bona fide EoE. As there are no known clinical predictors of EoE, all ARC007 participants will be approached about participating in this sub-study. Further analyses will be conducted on those subjects who develop GI symptoms during the course of OIT and controls who do not develop GI symptoms. While all subjects will provide baseline saliva specimens (collected at screening), the collection of esophageal specimens may provide additional supportive data. Specifically, if subjects in the study withdraw from OIT and undergo a clinically-indicated EGD, whenever possible, biopsy material will be collected from the site for further analysis, as per the ARC007 protocol.

In addition to addressing the detection of bio-molecular signatures in subjects having AEs, it is possible that specific bio-molecular signatures could emerge from the planned study that associate with treatment success or treatment withdrawal. Thus, a possibility exists that the proposed bio-specimen testing could yield biomarkers predictive of an individual subject's response to OIT and the collection of bio-specimens in this sub-study could facilitate these future analyses.

## Known and Potential Risks and Benefits to Human Participants

### Risks

The principal potential risk associated with this sub-study is the potential for emotional or psychological distress related to the discovery of uncertain information that is not itself diagnostic but may suggest a new clinical diagnosis (ie, EoE). To mitigate against this risk, and because the assays run in this sub-study are experimental, exploratory, and not part of standard care EoE diagnostics, the results of these studies will not be shared with participants. Clinical management of these individuals will be at the judgment of the site Investigator, per the current standard of care. The ARC007 protocol also contains specific recommendations about the clinical follow-up of subjects developing GI AEIs. All study candidates entering ARC007 will undergo an informed consent procedure detailing the potential risk of OIT-associated GI symptoms, including the possibility of EoE.

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

### Benefits

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

## Objectives

### Primary Objective

The primary objective is to analyze bio-molecular expression patterns in saliva samples obtained longitudinally from peanut-allergic participants undergoing OIT in ARC007. These studies will target the salivary RNA transcriptome, and if necessary further validate, with molecular-, cellular-, and/or protein-based approaches, the expression profile of gene pathways that are likely relevant to intolerable GI side effects in ARC007 subjects.

### Secondary Objectives

The key secondary objective is to examine the relationship of the RNA expression profile to selected clinical variables from ARC007, including:

- The frequency and severity of AEs related to the GI tract
- The frequency of dosing interruptions (reductions and/or discontinuations) directly related to GI AEIs
- Peripheral blood eosinophil counts
- PEESS$^{TM}$ v2.0 scores
- Immunoglobulin levels (IgE, $IgG_4$, and their subclasses)

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

**Sub-study Design**

This is an optional sub-study in which samples will be obtained from ARC007 participants according to the SOE in the table presented below. Only subjects enrolled in ARC007 and providing additional consent for this sub-study are eligible to participate. Subjects enrolled in both ARC007 and this sub-study will undergo saliva collection coordinated at the designated ARC007 study visits. Otherwise these subjects will be treated according to the ARC007 study protocol.

**Sub-study Schedule of Events Exploratory Biochemical and Molecular Sub-study of Peanut-Allergic Children with Oral Immunotherapy-Related Gastrointestinal Symptoms in Study ARC007**

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

[a] Minimum study weeks are shown. Actual duration may be longer depending on subject's actual up-dosing in ARC007.
[b] For subjects who terminate dosing and enter observational follow-up, as per Section 7.3.4.2 of the ARC007 protocol. This sample is to be collected at the sixth monthly visit after study withdrawal or as close as practicable.
[c] Subjects withdrawing early from ARC007 with GI symptoms that were not already enrolled in this sub-study will be consented to enroll upon early termination.

Subjects in this sub-study will undergo 3 protocol-specified collections of saliva. All subjects will have a baseline saliva sample collected at Screening. Because the GI AEIs are unpredictable and treatment-emergent, the approach to sampling post-randomization will differ by treatment response. Subjects who develop GI-predominant AEs that prompt their withdrawal from ARC007 or a protracted disruption of dosing with IP will be considered cases in this sub-study. The second saliva sample will be collected from cases when the first PEESS v2.0 is completed. The final saliva sample for cases will be collected at the end of the protocol-defined 6-month follow-up period for subjects that withdraw from therapy.

Controls in this sub-study will be defined as ARC007 participants receiving OIT (active and placebo) who do not develop intolerable GI symptoms. Following the baseline collection, asymptomatic subjects will provide saliva samples at the 6-week up-dosing visit and again at the end of the up-dosing period.

This sub-study will principally involve collection, shipment, and banking of saliva samples at specified time points; gene expression analysis of selected salivary bio-specimens; and correlation with basic biometric data (eg, peripheral blood eosinophils, clinical symptom reports/PEESS v2.0 scores) obtained as necessary, and clinical outcome per the ARC007 protocol. Biochemical detection of eosinophil activation products or metabolites may also be possible from collected samples.

Subject participation will consist of signing an ICF approved by the IRB, EC, research ethics board, or like authority, and age-appropriate assent form, when indicated, as per local guidelines, and the provisions for bio-specimen collection and handling.

Case Definition: ARC007 Events Triggering PEESS v2.0

The following passage is taken from Section 7.3.4.2 of the ARC007 protocol, and serves to identify the case definition in this sub-study (eg, the ARC007 subjects who develop the GI AEIs requiring further evaluation).

Gastrointestinal AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered 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 who resumes dosing at a reduced dose level (Section 7.3.4.2 of the ARC007 protocol)
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus (Section 7.3.4.2 of the ARC007 protocol)
- Any subject who permanently discontinues dosing who had experienced GI AEs (Section 4.3.2 of the ARC007 protocol)

Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent/guardian, as appropriate, every month for 6 months. It should, however, be noted that the PEESS v2.0 was not designed to establish a diagnosis of EoE, and has not been validated for use in 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.

**Exploratory Endpoints**

All endpoints in this sub-study are considered exploratory. The objective is to characterize RNA expression patterns in salivary specimens collected from peanut-allergic subjects who

participated in a study of peanut OIT and developed intolerable GI AEs that interfered with treatment (ie, resulted in reducing, holding, or discontinuing OIT dose levels). ARC007 subjects who do not develop limiting GI symptoms will also be studied as control subjects. Secondarily, we will also examine the associations of the salivary RNA expression changes with selected clinical variables and explore the within-subject correlation to RNA expression patterns observed in esophageal specimens, when available.

**Bioinformatic Analysis Plan for Primary and Secondary Objectives**

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

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

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

**Criteria for Study Participation**

Inclusion Criteria

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

1. Participation in the ARC007 study
2. Written informed consent from the subject's parent/guardian
3. Written assent the subject as appropriate (eg, above the age of 7 years)

Exclusion Criteria

1. Otherwise ineligible for ARC007

Subject Termination from the Sub-study

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

Investigational Product

No IP will be administered in the sub-study.

Study Procedures

The following procedures will be performed:

1. Enrollment and Permissions
    - Obtain signatures on the IRB-approved ICF and subject's assent.
2. Sample Collection, Handling, and Analysis Procedures
    - Saliva is the principal bio-specimen to be collected in this study with the aid of a commercially available kit designed expressly for salivary RNA research purposes. Specific details for saliva collection will be provided to sites in a manual of procedures.
    - Blood samples for CBC, already collected in ARC007, will also be included in analyses relating to the secondary objectives of this sub-study.
    - Bio-specimens may be temporarily stored (no later than the next day) at investigational sites to facilitate batch shipping and receiving. All bio-specimens will be packaged and transported to the investigative laboratory in a manner compliant with all local, state, and federal laws and regulations, as per standard operating procedures of the shipping and receiving facilities.
    - Analyses will include one or more of the following:
        - Transcriptome analysis
        - EoE diagnostic panel comprising a 96-gene quantitative polymerase chain reaction (qPCR) array
        - Profiling of local cytokine expression
        - Targeted analysis of expression of previously identified specific candidate genes
        - Analysis of single nucleotide polymorphisms in previously identified specific candidate genes
        - Inflammatory pathway analysis (Ingenuity, Toppfun, or David)
        - qPCR analysis
        - Immunohistochemistry or other protein detection methods (eg, ELISA, Western blot, etc).
        - Mass spectrometry
        - Flow cytometry

Lead Investigative Laboratory

The lead investigative laboratory is the following:

Wen Lab – Cincinnati Children's Hospital Medical Center
S6.405 S Building
240 Albert Sabin Way
Cincinnati, OH 45242
USA

Permission to obtain samples of esophageal tissue from the residua (if any) of biopsy specimens will be obtained during the performance of routine clinical visit.

3. Safety Monitoring

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

4. Statistical Considerations

This sub-study is a pilot characterization of biochemical and bio-molecular markers in relation to GI side effects arising during peanut OIT in ARC007 subjects. The analyses to be conducted in this sub-study are all considered exploratory in nature. As such, descriptive statistical techniques will be utilized to characterize demographic and basic clinical variables, with standard assessments for normality and adjustments as necessary. Measures of correlation and longitudinal repeated measures will be assessed with appropriate techniques (eg, regression modeling) as necessary. Statistical testing for differences between treatment groups or time points may be assessed, but specific hypotheses are not pre-specified.

5. Study Endpoint Assessment

All endpoints in this study are considered exploratory and are defined in the Objectives section of this Appendix 7 above.

6. Subject and Demographic Data

Baseline Characteristics, Demographics, and Safety Data

Baseline and demographic characteristics may be reported for each subject enrolled in the present study as they were obtained in ARC007. Baseline characteristics and demographic data could include age, race, sex, body weight, and height. Other analyses involving safety data may also be performed.

Use of Medications

There will be no medications used in this sub-study. Data from concomitant medication use in ARC007 related to AEs may be analyzed as part of this sub-study.

7. Sample Size Calculations

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

## Appendix 8: Total Nasal Symptom Score Sheet (Example)

**TOTAL NASAL SYMPTOM SCORE**

**PLEASE ANSWER ALL QUESTIONS TO THE BEST OF YOUR ABILITY.** This information will assist us in understanding and treating your symptoms.

| 1. Please rate how your **nasal congestion** has been over the past: | 12 hours | Last 2 weeks |
|---|---|---|
| None | 0 ○ | 0 ○ |
| Mild (symptom clearly present but easily tolerated) | 1 ○ | 1 ○ |
| Moderate (symptom bothersome but tolerable) | 2 ○ | 2 ○ |
| Severe (symptom difficult to tolerate – interferes with activities) | 3 ○ | 3 ○ |

| 2. Please rate how your **runny nose** has been over the past: | 12 hours | Last 2 weeks |
|---|---|---|
| None | 0 ○ | 0 ○ |
| Mild (symptom clearly present but easily tolerated) | 1 ○ | 1 ○ |
| Moderate (symptom bothersome but tolerable) | 2 ○ | 2 ○ |
| Severe (symptom difficult to tolerate – interferes with activities) | 3 ○ | 3 ○ |

| 3. Please rate how your **nasal itching** has been over the past: | 12 hours | Last 2 weeks |
|---|---|---|
| None | 0 ○ | 0 ○ |
| Mild (symptom clearly present but easily tolerated) | 1 ○ | 1 ○ |
| Moderate (symptom bothersome but tolerable) | 2 ○ | 2 ○ |
| Severe (symptom difficult to tolerate – interferes with activities) | 3 ○ | 3 ○ |

| 4. Please rate how your **sneezing** has been over the past: | 12 hours | Last 2 weeks |
|---|---|---|
| None | 0 ○ | 0 ○ |
| Mild (symptom clearly present but easily tolerated) | 1 ○ | 1 ○ |
| Moderate (symptom bothersome but tolerable) | 2 ○ | 2 ○ |
| Severe (symptom difficult to tolerate – interferes with activities) | 3 ○ | 3 ○ |

| 5. Please rate how **difficult sleep** has been with nasal symptoms: | Last night | Last 2 weeks |
|---|---|---|
| None | 0 ○ | 0 ○ |
| Mild (symptom clearly present but easily tolerated) | 1 ○ | 1 ○ |
| Moderate (symptom bothersome but tolerable) | 2 ○ | 2 ○ |
| Severe (symptom difficult to tolerate – interferes with activities) | 3 ○ | 3 ○ |

**TOTAL SCORE:** 0 / 0