CLINICAL STUDY PROTOCOL

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

Protocol Amendment 3 – 15 Aug 2017
Reference Numbers: NCT02198664, EudraCT 2021-002533-42

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CLINICAL STUDY PROTOCOL

Protocol Title:	Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen CPNA) Peanut Oral Immunotherapy (OIT) Safety Follow-On Study
Investigational Drug:	AR101 [Characterized Peanut Allergen (CPNA)]
Protocol Number:	ARC002
IND Number:	IND 15463
Sponsor:	Aimmune Therapeutics, Inc. (Previously Allergen Research Corporation) 8000 Marina Blvd., Suite 300 Brisbane, CA 94005 USA
Version:	Amendment 3 Supersedes 2.0 Amendment 2
Date:	15 August 2017

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Sponsor Protocol Approval

Protocol ARC002	Version/Date: Amendment 3 / 15 August 2017
Sponsor: Aimmune Therapeutics, Inc. [Previously Allergen Research Corporation (ARC)]	
Short Title: CPNA Peanut OIT Follow-On	

I have read protocol ARC002 Amendment 3, and I approve it. I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Daniel C. Adelman, MD

Chief Medical Officer (Print)

Chief Medical Officer (Signature)

August 18, 2017

Date

Principal Investigator Protocol Approval

Protocol ARC002	Version/Date: Amendment 3 / 15 August 2017
IND: 15463	Principal Investigator:
Short Title: CPNA Peanut OIT Follow-On	

I have read protocol ARC002 Amendment 3, and I approve it. As the principal investigator, I agree to conduct this protocol according to Good Clinical Practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance" *(April 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

Synopsis

Protocol ARC002 Amendment 3 Synopsis	
Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT) Safety Follow-On Study**
Short Title	CPNA Peanut OIT Follow-On
Clinical Phase	2
IND	15463
IND Sponsor	Aimmune Therapeutics, Inc. [Previously Allergen Research Corporation (ARC)]
Number of Subjects	Up to approximately 50 peanut-allergic subjects who complete ARC001 and consent to participate in ARC002 will be enrolled
Objective	The primary objective is to assess the safety and tolerability of AR101 [Characterized Peanut Allergen (CPNA)] when used in an oral immunotherapy (OIT) paradigm over an extended period (≥ 18 months) in peanut-allergic children and young adults who initiated OIT between the ages of 4 to 26 years, inclusive. The secondary objectives are: • To confirm and extend prior observations from ARC001 on the efficacy of Characterized Peanut Allergen in OIT, as assessed through reduction in clinical reactivity to limited amounts of peanut allergen. Specifically: o To assess the efficacy of OIT in inducing desensitization of allergic responses to peanut in the former placebo subjects from ARC001 (Group 1) challenged with peanut flour in a double-blind placebo-controlled food challenge (DBPCFC) after approximately 6 months of open-label treatment. o To assess the efficacy of OIT in sustaining and/or enhancing desensitization of allergic responses to peanut in the former active AR101 (CPNA) treatment subjects from ARC001 (Group 2) and the former placebo subjects from ARC001 (Group 1) challenged with peanut flour in a DBPCFC after approximately 3 additional months of open-label treatment. • To evaluate the immunological effects of peanut OIT • To determine the time course of tolerated up-dosing • To evaluate safety based on physician global assessment of disease activity The exploratory objective is to assess a higher degree of desensitization, based on an Open-label Food Challenge (OFC) up to a cumulative dose of 4043 mg of total peanut protein.
Study Design	This is a multi-center, open-label, follow-on study to gather additional information on the safety and tolerability of oral desensitization with AR101 (CPNA) in the subjects who participated in ARC001. **Group 1:** Subjects who complete the placebo arm of ARC001 and consent to enroll in ARC002 (Group 1) will cross over to active treatment using the same dosing regimen used in ARC001, but in open-label fashion. They will undergo a 2- to 3-day Initial Escalation Phase, followed by an approximately 6-month (20- to 36-week) Low-dose Buildup Phase to 300 mg/d of peanut protein. They will maintain dosing at 300 mg/d for the last 2 weeks of this phase. After completion of the Low-dose Buildup Phase, Group 1 subjects will undergo a

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Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT) Safety Follow-On Study**
	DBPCFC (to a maximum of 600 mg of peanut protein). Subjects who fail to tolerate the post-Low-dose Buildup Phase DBPCFC at ≥ 300 mg will be considered escalation failures and will be discontinued from the study for safety considerations. Those subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein will enter an approximately 3-month (12- to 24-week) Plateau Phase of continued dosing at 300 mg/d. Following completion of the ~3-month Plateau Phase, Group 1 subjects will undergo a post-Plateau Phase DBPCFC (to a maximum of 1000 mg of peanut protein). Subjects who fail to tolerate the post-Plateau Phase DBPCFC at ≤ 30 mg will be discontinued from the study for safety considerations. Subjects who fail to tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg may, at the investigator's discretion, continue dosing in the Plateau Phase to a total of 24 weeks and undergo a repeat DBPCFC (See **Section 3.2.5** for details). Subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein will be given the option to increase further their daily dose of AR101 (CPNA) in an Optional High-dose Buildup Phase of approximately 10 to 30 weeks' duration. During this phase, the dose of peanut protein will be gradually increased at intervals of approximately 2 weeks to a target maximum of 2000 mg/d. After a daily dose of 2000 mg, or a subject's individual maximum tolerated dose (MTD), is achieved, subjects in Group 1 will continue in an Extended Maintenance Phase with AR101 (CPNA) until the Study Exit visit. Subjects who elect not to escalate their daily dose of AR101 (CPNA) above 300 mg of peanut protein will enter directly into the Extended Maintenance Phase. **Group 2:** Subjects who complete the active AR101 (CPNA) therapy arm of ARC001 and consent to enroll in ARC002 (Group 2) will enter directly into the 300 mg/d, ~3-month Plateau Phase of ARC002. That is, they will forego the ARC002 Initial Escalation Phase, Low-dose Buildup Phase, and post-Low-dose Buildup Phase DBPCFC, having completed these in ARC001. The procedures followed for Group 2 subjects for the Plateau Phase, post-Plateau Phase DBPCFC, Optional High-dose Buildup Phase, and Extended Maintenance Phase will be the same as for Group 1. This study will be terminated in accordance with Protocol Amendment 3. Upon IRB approval of Protocol ARC008 and at the time of IRB approval of Protocol Amendment 3 at the study site, all subjects remaining on study will be asked to return to the study center to complete the Study Exit visit where they will have the option to undergo an OFC to a maximum cumulative dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008. A Data Monitoring Committee (DMC) will monitor the study for safety.
Study Duration	Subjects in Group 1 are expected to reach the Extended Maintenance Phase in approximately 36 weeks (but possibly as long as 90 weeks if dose adjustments are required); subjects in Group 2 are expected to reach the Extended Maintenance Phase in approximately 12 weeks (but possibly as long as 54 weeks if dose adjustments are required). Subjects may continue to participate in ARC002 after reaching the Extended Maintenance Phase where they will continue treatment with AR101 (CPNA) until the Study Exit visit, when they will have the option to undergo an OFC to a maximum cumulative

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Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT) Safety Follow-On Study**
	dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008.
Primary Endpoint	The primary end-point is the incidence of treatment-related adverse events and dosing symptoms occurring with peanut OIT over a protracted treatment period comprising at least 18 months.
Secondary Endpoints	• The proportion of subjects who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC • The proportion of subjects who tolerate at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC • The proportion of subjects who tolerate 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC • Change from baseline (carried over from ARC001) in maximum dose of peanut protein tolerated with no, or only mild, symptoms during DBPCFC • Maximum dose of peanut protein tolerated with no, or only mild, symptoms during DBPCFC • Changes in peanut-specific immunoglobulin E (IgE) and immunoglobulin G4 (IgG4), changes in skin prick test (SPT) mean wheal diameters will also be assessed. • Physician global assessment: Disease activity as measured on a 100 mm visual analogue scale (VAS)
Exploratory Endpoint	• The proportion of subjects who tolerate, with no more than mild symptoms, a Study Exit visit OFC to a cumulative dose of 4043 mg of peanut protein
Study Product and Design	AR101 [Characterized Peanut Allergen (CPNA)]. Doses characterized and normalized for total protein and specific peanut allergen ratios will ascend per the dosing regimens (refer to schedules provided at end of synopsis). Study product will be provided in break-apart capsules formulated to contain 0.5, 1.0, 10, 100, and 475 mg of peanut protein for administering doses of up to 2000 mg, inclusive. For doses ≥ 1000 mg, and for 300 mg dosing during the Extended Maintenance Phase, AR101 (CPNA) may alternatively be provided in foil sachets. A clinical site pharmacist will dispense study drugs to the investigational site in a manner consistent with the current dose level.
Inclusion Criteria	• Completion of study ARC001 • Written informed consent from subject and/or parent/guardian • Written assent from all subjects as appropriate • Use of birth control for females of child-bearing potential • No change in the status of any longitudinally applicable ARC001 inclusion criteria
Exclusion Criteria	• Early termination from ARC001 • For former active AR101 (CPNA) treatment subjects from ARC001 (Group 2), failure to tolerate with no or mild symptoms 300 mg of peanut protein in their ARC001 exit DBPCFC

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	• Pregnancy or lactation • For former placebo subjects from ARC001 (Group 1), a lapse in dosing of more than 10 days from completion of ARC001 • Change in the status of any longitudinally applicable ARC001 exclusion criteria
Treatment Description	All subjects will receive daily oral dosing of peanut OIT in the form of AR101 (CPNA). All escalation doses will occur in a Clinical Research Center (CRC) or monitored clinic setting under direct observation. **Group 1 (former ARC001 placebo subjects) only:** Initial Escalation Phase (2 or 3 days): Eligible Group 1 subjects will initiate OIT starting at a dose of 0.5 mg of peanut protein, and then increase the dose incrementally at 20 to 30 minute intervals over the course of a single day to a maximum dose of 6 mg. Subjects who fail to tolerate at least a 3 mg dose will be considered escalation failures. Subjects who either tolerate both the 3 mg and 6 mg dose of peanut protein, or who tolerate the 3 mg, but not the 6 mg dose, will undergo confirmatory testing of their highest tolerated dose (not exceeding 6 mg) over the subsequent 1 or 2 days (refer to Initial Escalation Schedule at end of synopsis). Therapy details are found in **Section 3** and **Section 6** of the protocol. Low-dose Buildup Phase (~6 months): Group 1 subjects will embark on a dose-escalation regimen, with the dose of peanut protein being gradually increased at intervals of approximately 2 weeks to a maximum of 300 mg/d (refer to Low-dose Buildup Schedule at end of synopsis). After successfully escalating to a 300 mg daily dose, subjects will maintain that dose level for an additional 2 weeks. Therapy details are found in **Section 3** and **Section 6** of the protocol. Group 1 subjects unable to achieve a dose of 300 mg/d of peanut protein by 34 weeks will be considered escalation failures. Post-Low-dose Buildup Phase DBPCFC: After completing 2 weeks of dosing at 300 mg/d, Group 1 subjects will undergo a DBPCFC. This post-Low-dose Buildup Phase DBPCFC will be performed in accordance with PRACTALL (PRACTical issues in ALLergology Joint United States/European Union Initiative) guidelines, but requiring progression in an unaltered sequence **Table 6-1** without repeating any dose. The procedure will also be modified in that the top dose will be capped at 600 mg (1043 mg cumulative) peanut protein or placebo. Group 1 subjects who fail to tolerate the post-Low-dose Buildup DBPCFC at the 300 mg (443 mg cumulative) protein level with no, or only mild, symptoms will be considered escalation failures, will not be eligible to proceed to the ~3-month Plateau Phase, and will be discontinued from the study. **Group 1 and Group 2:** Plateau Phase (~3 months): Eligible subjects (Group 1 and Group 2) will receive peanut OIT at a daily dose of 300 mg of peanut protein for about 3 months (although the period may be extended to as long as 24 weeks on an individual basis if dose adjustments are required).

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	Post-Plateau Phase DBPCFC: Following the Plateau Phase, subjects will undergo a post-Plateau Phase DBPCFC, performed in the same manner as the post-Low-dose Buildup Phase DBPCFC, but with escalation capped at 1000 mg (2043 mg cumulative) of peanut protein or placebo. Optional High-dose Buildup Phase (approximately 10 to 30 weeks): Supplemental informed consent (and assent, as age appropriate) will be obtained from subjects (or parent/guardian, as age appropriate) prior to entering the Optional High-dose Buildup Phase. Subjects who do not consent to the Optional High-Dose Buildup Phase will enter directly into the Extended Maintenance Phase where they will continue to receive daily OIT dosing with 300 mg of peanut protein as AR101 (CPNA) for the duration of the study. Subjects who do consent to the Optional High-Dose Buildup Phase will embark on a dose-escalation regimen, starting at a dose based on the highest dose tolerated in the post-Plateau Phase DBPCFC. They will return to the CRC on the day after the post-Plateau Phase DBPCFC to confirm the tolerability of the highest dose tolerated in the post-Plateau Phase DBPCFC. They will then continue at this dose level with daily home-dosing for 2 weeks. Thereafter, doses will be gradually increased at intervals of approximately 2 weeks to a target maximum of 2000 mg/d of peanut protein (refer to High-dose Buildup Schedule at end of synopsis). Escalation to each new dose level will be conducted under direct observation in the CRC. Therapy details are found in **Section 3** and **Section 6** of the protocol. Extended Maintenance Phase: Subjects who do not consent to the Optional High-dose Buildup Phase will enter directly into the Extended Maintenance Phase and continue dosing at 300 mg/d. Subjects who do consent to the Optional High-dose Buildup Phase will enter the Extended Maintenance Phase and continue dosing at 2000 mg/d, or the subject's individual MTD until the Study Exit visit. Upon IRB approval of Protocol ARC008 and at the time of IRB approval of Protocol Amendment 3 at the study site, all subjects remaining on study will be asked to return to the study center to complete the Study Exit visit where they will have the option to undergo an OFC to a maximum cumulative dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008.
Study Procedures	The following procedures will be performed according to: **Appendix 1**: Schedule of Events. • Informed consent • Inclusion/exclusion criteria • Confirm treatment assignment, full-duration study participation, and results of exit DBPCFC from ARC001 • Concomitant medications • Physical exam, including height and weight • Vital signs: blood pressure (BP), pulse rate (PR), temperature • Peak Expiratory Flow Rate (PEFR) • Pregnancy test • Interval diet and allergy history

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	• Blood draw for peanut specific IgE and IgG4 • Optional blood draw (pre-DBPCFC and 5-10 days post-DBPCFC) for exploratory analyses by the Immune Tolerance Network (ITN)/Benaroya • Skin prick test (SPT) • Drug administration in the CRC • Dispensing of study drugs for home dosing/Return of unused drugs • Dose assessment to determine maintenance or up-dosing • Peak Expiratory Flow Rate (PEFR) prior to any DBPCFC • Double-blind, placebo controlled food challenge (DBPCFC) in accordance with PRACTALL guidelines • Open-label food challenge (OFC) in accordance with PRACTALL guidelines • Physician Global Assessment of Disease Activity • Monitoring for dosing compliance and symptoms • Adverse event (AE) monitoring • Telephone follow-up to assess dosing compliance and symptoms • EQ-5D-5L Questionnaire • TSQM-9 Questionnaire • Parent/Patient Exit Survey • Peanut Allergy Interview

Protocol ARC002 Synopsis			
Initial Escalation Schedule for Peanut OIT (Group 1 subjects only)			
Dose Level # since Baseline (ARC001)	**Study Product Dose (mg peanut protein)**	**Cumulative Study Product Dose (mg peanut protein)**	**% Increase**
1	0.5	0.5	
2	1.0	1.5	100%
3	1.5	3.0	50%
4	3.0	6.0	100%
5	6.0	12	100%
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. Day 1: Subjects who are unable to tolerate a dose of 3 mg at the end of Day 1 will be considered escalation failures. Subjects who tolerate at least 3 mg on Day 1 will return on Day 2 to receive their highest tolerated dose (3 mg or 6 mg). Day 2: Subjects with either no symptoms or mild symptoms on Day 2 (at either 3 mg or 6 mg) will start daily home dosing at their highest tolerated level. Day 3: Subjects who experience moderate or severe symptoms after receiving a 6 mg dose on Day 2 will return on Day 3 to receive the next lower dose (3 mg). Subjects with moderate or severe symptoms at 3 mg on either Day 2 or Day 3 will be considered escalation failures.			
Low-dose Buildup Schedule for Peanut OIT (Group 1 subjects only)			
Dose Level # since Baseline (ARC001)	**Study Product Dose (mg peanut protein)**	**Interval (weeks)**	**% Increase**
6	12	2	
7	20	2	67%
8	40	2	100%
9	80	2	100%
10	120	2	50%
11	160	2	33%
12	200	2	25%
13	240	2	20%
14	300	2	25%
Dose escalations will occur every 2 weeks, with dose increases administered in the CRC under direct observation. Capsules are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.			

Optional High-dose Buildup Schedule for Peanut OIT (Groups 1 & 2 subjects)			
Dose Level # since Baseline (ARC001)	**Study Product Dose (mg peanut protein)**	**Interval (weeks)**	**% Increase**
15	400	2	33%
16	475	2	25%
17	575	2	20%
18	775	2	33%
19	950	2	23%
20	1250	2	20%
21	1425	2	25%
22	1625	2	22%
23	2000	2	23%

Note: Subjects will embark on the High-dose Buildup Phase Schedule based on the highest dose tolerated in the post-Plateau Phase DBPCFC. This could vary on an individual basis between 300 mg and 1000 mg, inclusive.

Capsules, or sachets, are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.

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Glossary of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme inhibitors
AE	Adverse Event
ARB	Angiotensin-receptor blockers
ARC	Allergen Research Corporation
BP	Blood Pressure
CFR	US Code of Federal Regulations
CoFAR	Consortium of Food Allergy Research
CPNA	Characterized Peanut Allergen
CRC	Clinical Research Center
CRF	Case Report Form
CRO	Contract Research Organization
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
DMC	Data Monitoring Committee
EAACI	European Academy of Allergy and Clinical Immunology
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EQ-5D-5L	Five Level EuroQol Five Dimensions Instrument
ER	Emergency Room
FDA	US Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second (spirometry)
FVC	Forced Vital Capacity
GCP / cGCP	Good Clinical Practice / Current Good Clinical Practice
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITN	Immune Tolerance Network
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes for Health
OIT	Oral Immunotherapy
OFC	Open-Label Food Challenge
PEFR	Peak Expiratory Flow Rate
PR	Pulse Rate

Abbreviation	Definition
PRACTALL	PRACTical issues in ALLergology Joint United States/European Union Initiative
Q	Latin term "quaque," meaning "every"
SAE	Serious Adverse Event
SPT	Skin Prick Test
TSQM-9	Treatment Satisfaction Questionnaire for Medication (9 Item)
VAS	Visual Analogue Scale
WHO	World Health Organization

1. Background and Rationale

1.1 Background

Peanut allergy is a common and serious condition that disproportionately affects children, and is commonly associated with severe reactions, including life-threatening anaphylaxis. The current standard of care in management of food allergy is dietary avoidance of the food, and education of the patient/family in the acute management of an allergic reaction. The burden of avoidance and constant fear of accidental exposure negatively affects the health-related quality of life for both subjects and their families.[1,2,3]

Currently, the only treatment for peanut allergy is a peanut-free diet and ready access to self-injectable epinephrine. However, strict avoidance diets can be complicated due to difficulty in interpreting food labels[4] and by the presence of undeclared or hidden allergens in commercially prepared foods.[5,6] Accidental ingestions are unfortunately common, with up to 50% of food-allergic patients having at least one allergic reaction over a two-year period.[7]

Allergic reactions to peanut can be severe and life-threatening; and peanut and/or tree nut allergies account for the vast majority of fatal food-induced anaphylaxis.[8] This combination of strict avoidance diets, the high incidence of accidental exposures, and the risk of severe or even fatal reactions with accidental exposures adds a tremendous burden and stress on patients and their families.

Specific immunotherapy for food allergy, in particular for peanut allergy, in the forms of oral immunotherapy (OIT) and sublingual immunotherapy, has been studied in recent years and has demonstrated encouraging safety and efficacy results in early clinical trials, including beneficial immunologic changes.[9-18] There is evidence that OIT may induce desensitization in most subjects, with immunologic changes over time indicating progression toward clinical tolerance.[15,19-22]

The goal of this program is to induce a state of desensitization to peanut protein defined as the absence of moderate or severe reaction following ingestion of a specific dose of peanut protein. This state of desensitization should be sufficient to protect a subject with peanut allergy from an accidental exposure to a small amount of peanut protein while maintaining a peanut-avoidant diet. Protection to a whole peanut, approximately 250 mg of peanut protein (measured as 500 mg of peanut flour), would afford a meaningful level of clinical protection against accidental exposure to peanut protein, since accidental exposures are typically to only small amounts of the allergen.[23]

1.2 Peanut OIT

Varshney et al[15] conducted a double-blind placebo-controlled study of an OIT protocol in subjects with severe allergy to peanut protein and consistently demonstrated an increase in the dose of allergen tolerated by the subjects versus baseline with a good safety profile.

In addition, peanut OIT has been administered under IND (Investigational New Drug Application) at Duke and Arkansas and under a separate IND at Stanford.† A total of 44 cases from Duke/Arkansas were analyzed and 14 cases from Stanford. Efficacy was demonstrated in 26 cases (17 active and 9 placebo) matching the published information. Sixteen out of 17 active subjects were escalated to a dose between 2400 and 4000 mg over a year. Oral food challenge results were significantly better for the active treatment group than the placebo group where both groups tolerated a mean of 12 mg of peanut protein at baseline, while at one year the mean for the active treatment group was 5000 mg of protein and for the placebo Group 180 mg of peanut protein ($P < 0.001$ by Wilcoxon rank-sum test).[15]

Dosing symptoms were typical for OIT protocols including rash, wheezing, rhinorrhea, sneezing, itching, abdominal pain, nausea, vomiting, and diarrhea. Symptoms were noted in both the active treatment and the placebo group. Of the 39 cases on active treatment, 4 doses of epinephrine were administered – 2 during dosing and 2 during double-blind, placebo controlled food challenges (DBPCFCs). The Stanford data reported on 14 subjects who were dosed with peanut OIT; the severity and rate of dosing symptoms were similar to those reported in the Duke/Arkansas data.

These published findings, along with the additional clinical data, are the basis for a Phase II trial to investigate peanut OIT for efficacy and safety in desensitizing peanut-allergic subjects. Protocol ARC001 was designed to be a double-blinded, placebo-controlled study establishing the efficacy of AR101 (CPNA) for conducting oral immunotherapy. Protocol ARC002 is an open-label protocol designed to demonstrate the safety of daily dosing with AR101 (CPNA) for an extended period (≥ 18 months), to confirm unblinded the efficacy of OIT with AR101 (CPNA) at a dose of 300 mg/d of peanut protein in the former ARC001 placebo population, to provide an option to explore unblinded the safety and tolerability of AR101 (CPNA) doses as high as 2000 mg of peanut protein, and to maintain any desensitization that may have been achieved by subjects.

1.3 Rationale for Selection of Study Population

The primary objective of the ARC002 study is to assess the safety and tolerability of AR101 (CPNA) when used in an OIT paradigm over an extended period (≥ 18 months) in peanut-allergic children and young adults. The main secondary objective is to confirm and extend prior observations from ARC001 on the efficacy of AR101 (CPNA) in OIT. To achieve these objectives, the study will enroll up to approximately 50 subjects with a history of allergy to peanuts or peanut-containing foods who successfully completed the ARC001 study. Subjects who did not successfully complete ARC001, either because of early discontinuation (regardless of treatment assignment), or who were unable to tolerate with no or mild symptoms 300 mg of

† Data, provided courtesy of Wesley Burks of the University of North Carolina (formerly of Duke University Medical Center), Stacie Jones of University of Arkansas for Medical Sciences, and Kari Nadeau of Stanford University School of Medicine, on file at Allergen Research Corporation and summarized in a report, "Study Report for Clinical Trial Data Collected Under IND for Peanut Oral Immunotherapy," prepared by a third-party vendor, The EMMES Corporation (Rockville, MD)

peanut protein in the exit DBPCFC (for subjects assigned to the active treatment arm only) will be excluded from enrolling in ARC002 for safety considerations.

1.4 Rationale for Selection of Study Drug Regimen

The rationale for dosing builds on the work of the Consortium of Food Allergy Research (CoFAR) and its investigators and follows the same dosing strategy used in ARC001. In ARC001, the dosing consisted of a single-day initial escalation at very low doses, followed by a buildup phase of dose escalation, with a dose-escalation occurring every 2 weeks. This approach was demonstrated to be well-tolerated and efficacious in previous studies and will be used in this current trial.[24] For the subjects rolling over to ARC002 from the placebo arm of ARC001 (Group 1 subjects), the same dosing regimen used in the active treatment arm of ARC001 will be employed at the start of ARC002, but in an open-label fashion. This regimen consists of an Initial Escalation Phase, a Low-dose Buildup Phase, and a DBPCFC to 600 mg of peanut protein. Following the same procedures (with the exception of blinding) as used for the active treatment arm in ARC001 will permit confirmation of key findings from ARC001 in a second cohort of subjects.

After successful completion of the Initial Escalation Phase, Low-dose Buildup Phase, and post-Low-dose Buildup Phase DBPCFC to 600 mg of peanut protein, Group 1 subjects will enter into an approximately 3-month Plateau Phase, wherein the daily dose of AR101 (CPNA) peanut protein will remain at 300 mg. Subjects rolling over to ARC002 from the active treatment arm of ARC001 (Group 2 subjects) will not repeat the Initial Escalation Phase, Low-dose Buildup Phase, and post-Low-dose Buildup Phase DBPCFC, which were already undertaken in ARC001, but instead will enter directly into the ~3-month Plateau Phase. The Plateau Phase will permit assessment of the tolerability of the 300 mg dose, slightly more peanut protein than an average peanut kernel, over an extended length of time. Moreover, with the inclusion of a 600 mg and a 1000 mg dose level in the post-Plateau Phase DBPCFC, information as to whether the level of desensitization might improve with continued daily exposure to sub-gram quantities of peanut protein will be gained. At present, the role of protracted exposure to relatively low (sub-gram) quantities of peanut protein in promoting desensitization cannot be ascertained from the medical literature with any degree of certainty, neither in terms of duration nor dose. Maintenance phases reported for OIT procedures have varied in duration from a few weeks to more than 7 years; and maintenance doses have ranged from 300 to 8000 mg.[15,19,20,25-27] For those studies reporting oral food challenges after a maintenance phase, the range in maintenance dose has been from 300 to 4000 mg, and the range in durations has been from 6 weeks to 22 months.[15,19,20,25,26]

After successful completion of the 3- to 6-month 300 mg/d Plateau Phase and DBPCFC, all subjects (Group 1 and Group 2) will be given the option to increase their daily dose of AR101 (CPNA) peanut protein incrementally to a target maximum of 2000 mg/d, by consenting to enter an Optional High-dose Buildup Phase. The procedures to be followed during this optional phase adhere to the same principles as for the Low-dose Buildup Phase and are consistent with those advanced by CoFAR. Subjects who do not consent to the Optional High-dose Buildup Phase will enter directly into the Extended Maintenance Phase.

Allowing for a high-dose option is considered important, as the optimal dose of peanut protein for maintaining desensitization remains unknown. Moreover, there may, in fact, be no single optimal dose for maintaining desensitization, as desensitization is not an absolute, but rather a

relative, state, one that may depend on the level of accidental exposure, the immunologic and genetic makeup of the person exposed, and the environment in which the exposure occurs, both external and internal. Nevertheless, there is the possibility that higher levels of daily exposure may protect against higher levels of accidental exposure; thus, it may be of value to offer peanut-allergic patients more than one OIT dosing option. The Optional High-dose Buildup Phase will provide basic safety and tolerability information that will lay the groundwork for developing a high-dose treatment option, should such an option be pursued.

Following the Optional High-dose Buildup Phase, both Group 1 and Group 2 subjects will enter an Extended Maintenance Phase, wherein they will continue to take their maximum tolerated dose (MTD), up to 2000 mg/d, until the Study Exit visit when they will have the option to undergo an OFC to a maximum cumulative dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008. This is to allow all subjects to maintain any desensitization that may have been achieved.

1.5 Rationale for the Dose Used for the DBPCFC

The study DBPCFCs will be conducted in accordance with the recommended PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) consensus guidelines,[28] although the DBPCFC performed after the Low-dose Buildup Phase in Group 1 (former ARC001 placebo) subjects will not go above a 600 mg (1043 mg cumulative) dose to help ensure patient safety. This DBPCFC will assess protection against slightly more than 1 peanut's worth of peanut protein, 300 mg (443 mg cumulative dose), inasmuch as accidental exposures typically occur to limited amounts of allergen. Group 1 subjects who fail to tolerate with no or mild symptoms the 300 mg dose will not progress further in the DBPCFC and will undergo early termination from the study. To assess further desensitization, patients tolerating the 300 mg (443 mg cumulative) incremental dose in the DBPCFC will also be challenged with a 600 mg dose (cumulative 1043 mg). They will not receive the 3000 mg dose (4443 mg cumulative) outlined in the PRACTALL guidance, since at this point they will have been up-dosed only to the 300 mg dose level and maintained at that level for just 2 weeks.

The DBPCFC performed after the ~3-month, 300 mg/d, Plateau Phase in all subjects (both Group 1 and Group 2) will also assess protection against slightly more than 1 peanut's worth of peanut protein, i.e., 300 mg (443 mg cumulative dose). It will be of interest to observe whether a greater proportion of subjects tolerate the 300 mg dose with no symptoms versus mild symptoms in this DBPCFC as compared to the ARC001 exit (or ARC002 post-Low-dose Buildup Phase) DBPCFC. By the time the DBPCFC is administered after the Plateau Phase, all subjects should have been tolerating a daily dose of 300 mg routinely over a period of approximately 14 weeks. Subjects who fail to tolerate with no or mild symptoms the 30 mg dose in the post-Plateau Phase DBPCFC will be discontinued from the study due to safety considerations. Subjects who fail to tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg may, at the investigator's discretion, continue dosing in the Plateau Phase to a total of 24 weeks and undergo a repeat DBPCFC (See **Section 3.2.5** for details). To assess further desensitization, patients tolerating the 300 mg incremental (443 mg cumulative) dose will continue the DBPCFC with a 600 mg dose (cumulative 1043 mg), and, if that is tolerated, a final 1000 mg dose (cumulative 2043 mg). This represents a modification from PRACTALL guidelines in that a 600 mg incremental dose is

being added, and the top dose is being reduced from 3000 mg to 1000 mg in the interest of reducing safety risk. All subjects undergoing the post-Plateau Phase DBPCFC will have previously tolerated with no or mild symptoms a 300 mg challenge and been exposed to a 600 mg challenge.

To assess the maximum amount of desensitization, all subjects who consent at the end of their Extended Maintenance Phase, will undergo an optional OFC to a cumulative dose of 4043 mg of peanut protein at the Study Exit visit.

1.6 Known and Potential Risks and Benefits to Human Participants

1.6.1 Risks

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

In subjects with peanut allergy, there have been many oral immunotherapy studies performed using procedures and dosing similar to those proposed in this Phase 2 study. In general, the safety profile has been very good across the studies, and based on those studies, approximately 80%, 15%, and < 1% of the subjects are expected to have mild, moderate or severe symptoms, respectively, during some point in their dosing with the peanut OIT. It is important to note that essentially all adverse events have been allergy-related, predictable, and reversible. The major atypical adverse event from peanut OIT that has been reported in the literature is a single case of eosinophilic esophagitis, reversible upon stopping dosing.

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

Oral food challenges may induce an allergic response. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects have allergic reactions during the challenges, they may need oral, intramuscular, or intravenous medications, and will be treated per study center standard of care. Trained personnel, including a physician, as well as medications and equipment (per PRACTALL recommendations and investigational site standard operating procedures), will be immediately available to treat any reaction. The anticipated rate of serious life-threatening anaphylactic reactions would be < 0.1%.

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; and subjects in the trial and their participating family will be warned that they should continue to practice their usual vigilance against

accidental ingestion of peanuts or peanut-containing foods (please refer to the current AR101 (CPNA) Investigator's Brochure).

1.6.2 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.

2. Objectives

2.1 Primary Objective

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

2.2 Secondary Objective(s)

The secondary objectives are:

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

2.3 Exploratory Objective

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

3. Study Design

ARC002 is a multi-center, open-label, follow-on study to gather additional information on the safety and tolerability of oral desensitization with AR101 (CPNA) in the subjects who participated in ARC001. The study design is illustrated in **Figure 3-1**, **Figure 3-2**, and **Figure 3-3**.

Group 1:

Subjects who complete the placebo arm of ARC001 and consent to enroll in ARC002 (Group 1) will cross over to active treatment using the same dosing regimen used in ARC001, but in open-label fashion. They will undergo a 2- to 3-day Initial Escalation Phase, followed by an approximately 6-month (20- to 36-week) Low-Dose Buildup Phase to 300 mg/d of peanut protein. They will maintain dosing at 300 mg/d for the last 2 weeks of this phase. After completion of the Low-dose Buildup Phase, Group 1 subjects will undergo a DBPCFC (to a maximum of 600 mg of peanut protein). Subjects who fail to tolerate the post-Low-dose Buildup Phase DBPCFC at ≥ 300 mg will be considered escalation failures and will be discontinued from the study for safety considerations (**Figure 3-1**).

Those subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein will enter an approximately 3-month (12- to 24-week) Plateau Phase of continued dosing at 300 mg/d. Following completion of the ~3-month Plateau Phase, Group 1 subjects will undergo a post-Plateau Phase DBPCFC (to a maximum of 1000 mg of peanut protein). Subjects who fail to tolerate the post-Plateau Phase DBPCFC at ≤ 30 mg will be discontinued from the study for safety considerations (**Figure 3-1**). Subjects who fail to tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg may, at the investigator's discretion, continue dosing in the Plateau Phase to a total of 24 weeks and undergo a repeat DBPCFC (See **Section 3.2.5** for details).

Subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein will be given the option to increase further their daily dose of AR101 (CPNA) in an Optional High-dose Buildup Phase of approximately 10 to 30 week's duration. During this phase, the dose of peanut protein will be gradually increased at intervals of approximately 2 weeks to a target maximum of 2000 mg/d. After a daily dose of 2000 mg, or a subject's individual maximum tolerated dose (MTD), is achieved, subjects in Group 1 may continue in an Extended Maintenance Phase. Subjects who elect not to escalate their daily dose of AR101 (CPNA) above 300 mg of peanut protein will enter directly into the Extended Maintenance Phase (**Figure 3-3**).At the end of this period, subjects will complete a Study Exit visit. At this visit, subjects will be offered the option of an OFC to a maximum cumulative dose of 4043 mg of peanut protein.

Group 2:

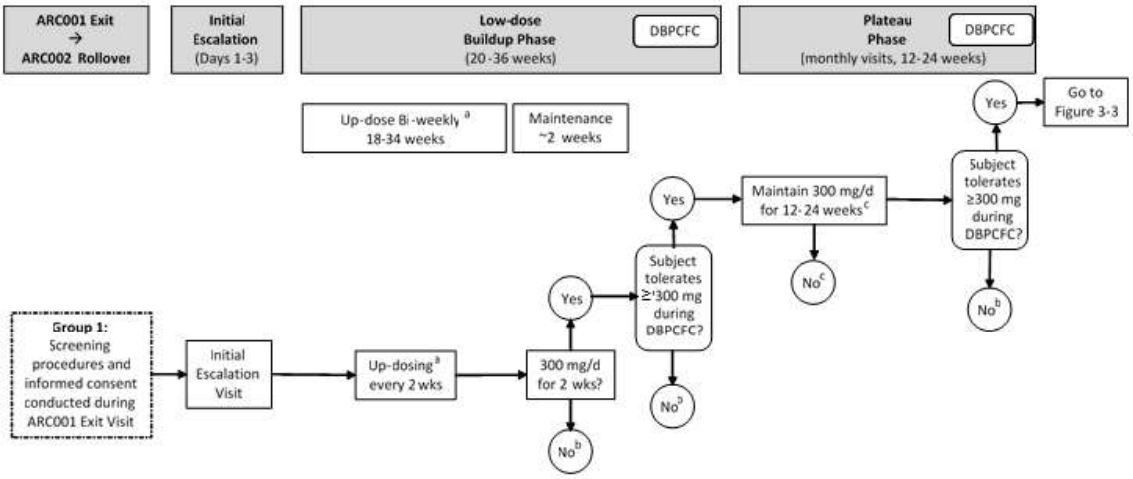
Subjects who complete the active AR101 (CPNA) therapy arm of ARC001 and consent to enroll in ARC002 (Group 2) will enter directly into the 300 mg/d, ~3-month, Plateau Phase of ARC002 (**Figure 3-2**). That is, they will forego the ARC002 Initial Escalation Phase, Low-dose Buildup Phase, and post-Low-dose Buildup Phase DBPCFC, having completed these in ARC001. The procedures followed for Group 2 subjects for the Plateau Phase, post-Plateau Phase DBPCFC, Optional High-dose Buildup Phase, and Extended Maintenance Phase will be the same as for Group 1 (**Figure 3-2** and **Figure 3-3**). Subjects in Group 2 will also undergo a Study Exit visit

at the completion of the Extended Maintenance Phase, same as for Group 1 subjects, and all subjects will be offered the option of the OFC at a maximum cumulative dose of 4043 mg of peanut protein.

This study will be terminated in accordance with Protocol Amendment 3. At the time of IRB approval of Protocol Amendment 3 at the study site, all subjects remaining on study will be asked to return to the study center to complete the Study Exit visit where they will have the option to undergo an OFC to a maximum cumulative dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008.

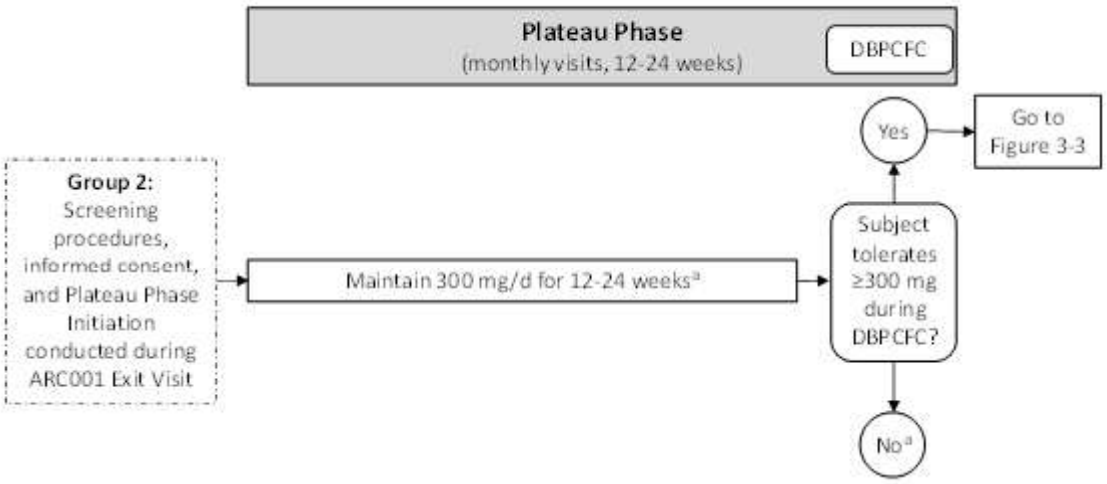
A Data Monitoring Committee (DMC) will monitor the study for safety.

Figure 3-1: Study Design, Group 1: Screening – Plateau Phase



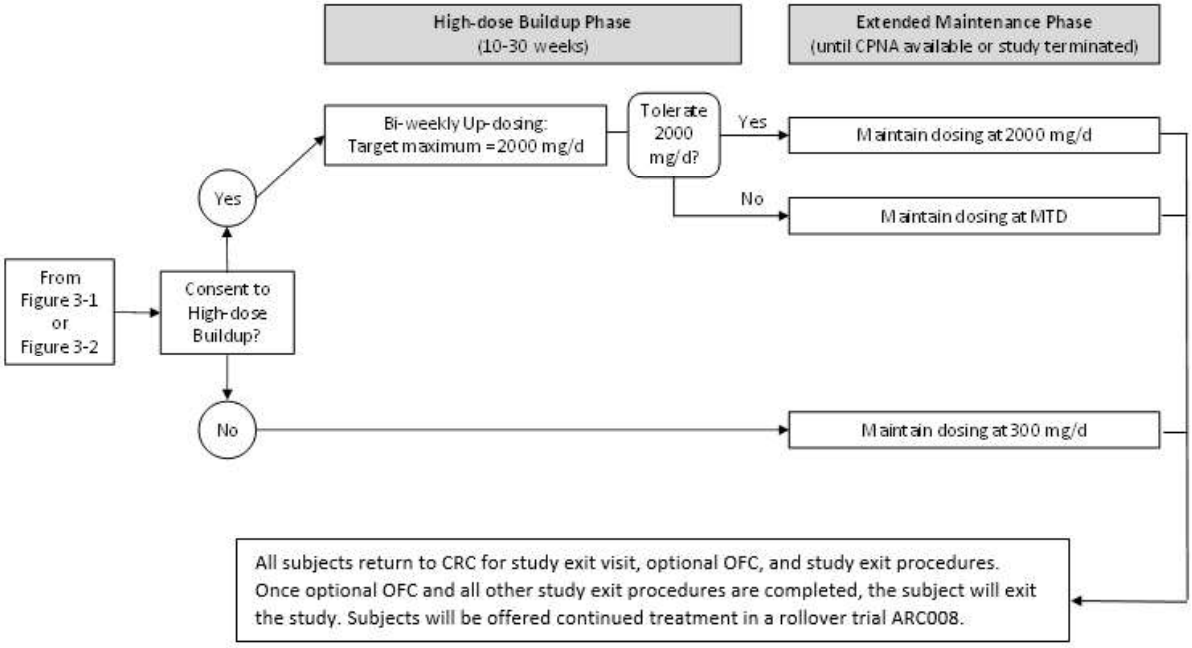
a: Dose escalation performed under direct observation in the CRC
b: Subjects who do not reach a dose of 300 mg/d by Week 34 of the Low- dose Buildup Phase, or who fail to tolerate the post Low-dose Buildup Phase DBPCFC at ≥ 300 mg, or the post-Plateau Phase DBPCFC at ≤ 30 mg, are considered escalation failures and discontinued from the study. Subjects who fail to tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg may, at the investigator's discretion, continue in the Plateau Phase to a total of 24 weeks and undergo a repeat DBPCFC (See text of **Section 3.2.5** for details).
c: Subjects who have not been able to tolerate 300 mg/d for the last 4 weeks of the Plateau Phase or had more than 2 dose reduction episodes during the phase are considered escalation failures and discontinued from the study

Figure 3-2: Study Design, Group 2: Screening – Plateau Phase



a: Subjects who have not been able to tolerate 300 mg/d for the last 4 weeks of the Plateau Phase, or had more than 2 dose reduction episodes during the phase, or who fail to tolerate the post-Plateau Phase DBPCFC at ≤ 30 mg are considered escalation failures and discontinued from the study. Subjects who tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg may, at the investigator's discretion, continue in the Plateau Phase to a total of 24 weeks and undergo a repeat DBPCFC (See text of **Section 3.2.5** for details).

Figure 3-3: Study Design, Groups 1 and 2: Post-Plateau Phases



3.1 Rollover Visit

Screening for ARC002 will be conducted during the ARC001 Exit /ARC002 Rollover Visit. Procedures will consist of verifying that subjects satisfy all inclusion/ exclusion criteria,

confirming treatment assignment from ARC001, and obtaining informed consent from subjects or subjects' parent/guardian and subjects' informed assent, as age-appropriate. Medical, allergy, and concomitant medical history will also be updated. An interval medical examination will be performed, as well as Peak Expiratory Flow Rate (PEFR).*

Subjects in Group 2, formerly receiving active treatment in ARC001, will enter the Plateau Phase during this visit.

Subjects in Group 1, formerly receiving placebo in ARC001, will begin dosing in ARC002 approximately 5 to 10 days after the ARC001 Exit /ARC002 Rollover Visit.

3.2 Treatment Phases

The ARC002 study consists of a maximum of five phases as follows:

- Initial Escalation Phase
- Low-dose Buildup Phase
- Plateau Phase
- Optional High-dose Buildup Phase
- Extended Maintenance Phase

The former ARC001 placebo subjects (Group 1) will complete all five phases. The former ARC001 active AR101 (CPNA) treatment subjects (Group 2) will complete the last three.

For the former ARC001 placebo subjects (Group 1), treatment will comprise an Initial Escalation Phase (2 to 3 days), an ~6-month Low-dose Buildup Phase (20-36 weeks), an ~3-month Plateau Phase (12-24 weeks), an Optional High-dose Buildup Phase (10-30 weeks), and an Extended Maintenance Phase. The durations of the phases are described in terms of ranges or approximate lengths of time to allow for subjects who may require their dose-level to be held or reduced (within protocol-defined limits) during a particular phase of the study.

DBPCFCs will be performed at the end of the Low-dose Buildup Phase, at the end of the ~3-month Plateau Phase, and an optional OFC will be conducted at the end of the Extended Maintenance Phase (Study Exit visit).

Former ARC001 active AR101 (CPNA) treatment subjects (Group 2), will enter directly into the ~3-month Plateau Phase, followed by the post-Plateau Phase DBPCFC, the Optional High-dose Buildup Phase (10-30 weeks), and the Extended Maintenance Phase.

* If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.

Throughout the treatment phases, subjects will be monitored for tolerability as illustrated in **Figure 6-2** and **Figure 6-3**. If a subject is removed from therapy because of failing during the Initial Escalation, Plateau, or Buildup phases, the subject will continue to be followed for safety for 14 days following their last dose of AR101 (CPNA), at which time the subject is to return to the Clinical Research Center (CRC) for an Early Termination Visit.

Subjects who prematurely discontinue treatment for any other reason will also be brought in for an Early Termination Visit 14 days following their last dose of AR101 (CPNA).

All treatments will be conducted in open-label fashion. A clinical site pharmacist will prepare the study medications at different doses according to each subject's current dose-level.

A Data Monitoring Committee (DMC) has been established and will meet approximately every 3 months to monitor the study for safety.

3.2.1 Initial Escalation Phase (Group 1 only)

Eligible Group 1 subjects will initiate OIT starting at a dose of 0.5 mg of peanut protein, and then increase the dose incrementally at 20 to 30 minute intervals over the course of a single day to a maximum dose of 6 mg. Subjects who fail to tolerate at least a 3 mg dose will be considered escalation failures. Subjects who either tolerate both the 3 mg and 6 mg dose of peanut protein, or who tolerate the 3 mg, but not the 6 mg dose, will undergo confirmatory testing of their highest tolerated dose (not exceeding 6 mg) over the subsequent 1 or 2 days (refer to Initial Escalation table, **Table 3-1**, below).

Table 3-1: Initial Escalation Schedule for Peanut OIT (Group 1 subjects only)

Dose Level # since Baseline (ARC001)	Study Product Dose (mg peanut protein)	Cumulative Study Product Dose (mg peanut protein)	% Increase
1	0.5	0.5	NA
2	1.0	1.5	100%
3	1.5	3.0	50%
4	3.0	6.0	100%
5	6.0	12	100%

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.
Day 1: Subjects who are unable to tolerate a dose of 3 mg at the end of Day 1 will be considered escalation failures. Subjects who tolerate at least 3 mg on Day 1 will return on Day 2 to receive their highest tolerated dose (3 mg or 6 mg).
Day 2: Subjects with either no symptoms or mild symptoms on Day 2 (at either 3 mg or 6 mg) will start daily home dosing at their highest tolerated level.
Day 3: Subjects who experience moderate or severe symptoms after receiving a 6 mg dose on Day 2 will return on Day 3 to receive the next lower dose (3 mg).
Subjects with moderate or severe symptoms at 3 mg on either Day 2 or Day 3 will be considered escalation failures.

Group 2 subjects will not participate in the ARC002 Initial Escalation Phase, but instead will enter directly the ~3-month, 300 mg/d, Plateau Phase.

3.2.2 Low-dose Buildup Phase (Group 1 only)

After the Initial Escalation Phase (Days 1 to 3), Group 1 subjects will embark on a dose-escalation regimen, in which the dose of peanut protein will be gradually increased, at intervals of approximately 2 weeks, to a maximum of 300 mg/d of peanut protein as AR101 (CPNA). Subjects able to tolerate the up-dosing will report to the CRC every 2 weeks to escalate their OIT dose under direct observation, up to the expected daily dose of 300 mg. Group 1 subjects who successfully escalate to the 300 mg/d dose of peanut protein as AR101 (CPNA) will maintain daily dosing of 300 mg for an additional 2 weeks. The dosing escalation schedule is described in detail in **Table 3-2**, below (see also **Section 6**).

Table 3-2: Low-dose Buildup Schedule for Peanut OIT (Group 1 subjects only)

Dose Level # since Baseline (ARC001)	Study Product Dose (mg peanut protein)	Interval (weeks)	% Increase
6	12	2	NA
7	20	2	67%
8	40	2	100%
9	80	2	100%
10	120	2	50%
11	160	2	33%
12	200	2	25%
13	240	2	20%
14	300	2	25%

Dose escalations with occur every 2 weeks with dose increases administered in the CRC under direct observation.

Capsules are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.

Those Group 1 subjects who do not tolerate the target dose of 300 mg/d by 34 weeks will be considered escalation failures and will not undergo the post-Low-dose Buildup Phase DBPCFC. Group 2 subjects will not participate in the ARC002 Low-dose Buildup Phase, but instead will directly enter the ~3-month, 300 mg/d, Plateau Phase.

3.2.3 Post-Low-dose Buildup Phase DBPCFC (Group 1 only)

Group 1 subjects, who have been up-dosed to a 300 mg/d dose and have continued to receive that dose for at least 2 weeks, will undergo a DBPCFC. The post-Low-dose Buildup Phase DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in an unaltered sequence (**Table 6-1**) without repeating any dose. The procedure will also be modified in that the top dose will be capped at 600 mg (1043 mg cumulative) peanut protein or placebo.

Group 1 subjects who fail to tolerate with no or mild symptoms the post-Low-dose Buildup Phase DBPCFC at the 300 mg (443 mg cumulative) protein level will be considered escalation failures, will discontinue treatment, and complete an Early Termination Visit 14 days after the DBPCFC. Those subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein will enter the ~3-month Plateau Phase of continued dosing at 300 mg/d.

Group 2 subjects will not participate in the ARC002 post-Low-dose Buildup Phase DBPCFC, but instead will directly enter the ~3-month, 300 mg/d, Plateau Phase.

3.2.4 Plateau Phase (Group 1 and Group 2)

Eligible subjects from both Groups 1 and 2 will receive OIT at a dose of 300 mg/d of peanut protein for about 3 months (12 weeks). The Plateau Phase may, however, be extended to a maximum of 6 months (24 weeks) if dose-reduction and re-escalation is required during this phase.

3.2.5 Post-Plateau Phase DBPCFC (Group 1 and Group 2)

After ~3 months of peanut OIT at 300 mg/d, all subjects will undergo a DBPCFC. The post-Plateau Phase DBPCFC will be performed in accordance with PRACTALL guidelines in the same manner as the post-Low-dose Buildup Phase DBPCFC, except that a 600 mg dose will be added to the escalation sequence and escalation will be capped at 1000 mg (2043 mg cumulative) of peanut protein or placebo.

Subjects who fail to tolerate the post-Plateau Phase DBPCFC at ≤ 30 mg will be discontinued from the study for safety considerations. For subjects who fail to tolerate the post-Plateau Phase DBPCFC at 100 or 300 mg, the investigator should assess the subject for compliance with home dosing, the presence of AEs (unrelated to the DBPCFC), and other issues that may raise concerns about continued dosing (see **Section 4.3**). If, in the opinion of the investigator, it is safe for the subject to continue OIT, the subject may resume dosing for up to a total of 24 weeks in the Plateau Phase. If the subject can tolerate daily dosing at 300 mg for a minimum of 4 consecutive weeks, then a repeat DBPCFC is to be performed. This is intended to determine if desensitization has been maintained and to determine the dose at which the subject is eligible to enter the Optional High-dose Phase.

3.2.6 Optional High-dose Buildup Phase (Group 1 and Group 2)

Supplemental informed consent (and assent, as age appropriate) will be obtained from subjects (or parent/guardian) prior to entering the Optional High-dose Buildup Phase.

Subjects who do not consent to the Optional High-Dose Buildup Phase will enter directly into the Extended Maintenance Phase and continue to receive daily OIT dosing with 300 mg of peanut protein as AR101 (CPNA) for the duration of the study in the Extended Maintenance Phase.

Subjects who do consent to the Optional High-Dose Buildup Phase will embark on a dose-escalation regimen, based on the highest dose tolerated in the post-Plateau Phase DBPCFC (see **Figure 6-1**). They will return to the CRC on the day after the post-Plateau Phase DBPCFC to confirm the tolerability of the highest dose tolerated in the post-Plateau Phase DBPCFC. They will then continue at this dose level with daily home-dosing for 2 weeks. Thereafter, doses will be gradually increased at intervals of approximately 2 weeks to a target maximum of 2000 mg/d of peanut protein (refer to High-dose Buildup Schedule in **Table 3-3**, below). Escalation to each new dose level will be conducted under direct observation in the CRC.

Table 3-3 Optional High-dose Buildup Schedule for Peanut OIT

Dose Level # since Baseline (ARC001)	Study Product Dose (mg peanut protein)	Interval (weeks)	% Increase
15	400 mg	2	33%
16	475 mg	2	25%
17	575 mg	2	20%
18	775 mg	2	33%
19	950 mg	2	23%
20	1250 mg	2	20%
21	1425 mg	2	25%
22	1625 mg	2	22%
23	2000 mg	2	23%

Capsules, or sachets, are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.

3.2.7 Extended Maintenance Phase (Group 1 and Group 2)

After a daily dose of 2000 mg, or a subject's individual MTD of peanut protein, has been achieved and maintained for two consecutive weeks, subjects may continue in the Extended Maintenance Phase until study termination and the Study Exit visit.

3.3 Optional OFC at Study Exit Visit

This study will be terminated in accordance with Protocol Amendment 3. Upon IRB approval of Protocol ARC008 and at the time of IRB approval of Protocol Amendment 3 at the study site, all subjects remaining on study will be asked to return to the study center to complete the Study Exit visit where they will have the option to undergo an OFC to a maximum cumulative dose of 4043 mg of peanut protein. Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008.

Once the Study Exit visit is completed, the subject's participation in this study will cease and the subject may enroll in the ARC008 study and continue study treatment.

3.4 Study Design Safety Considerations

The study design includes important safety measures:

- All dose escalations will be supervised in the clinic
- The peanut OIT will only escalate to a maximum 6 mg single dose during the Initial Escalation Phase on Days 1-3 for the Group 1 subjects
- Dosing symptoms and adverse events will be captured throughout the study
- All subjects and/or their participating family (as appropriate for age and home circumstances) will be provided with an epinephrine auto-injector and will be trained in its use

- Subjects will be strongly cautioned against consuming any peanuts or peanut-containing foods while on study, and will be instructed to remain on a peanut-free diet.

3.5 Primary Endpoint

The primary end-point is the incidence of treatment-related adverse events and dosing symptoms occurring with peanut OIT over a protracted treatment period comprising at least 18 months.

3.6 Secondary Endpoints

- The proportion of subjects who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC
- The proportion of subjects who tolerate at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC
- The proportion of subjects who tolerate 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC
- Change from baseline (carried over from ARC001) in maximum dose of peanut protein tolerated with no, or only mild, symptoms during DBPCFC
- Maximum dose of peanut protein tolerated with no, or only mild, symptoms during DBPCFC
- Changes in peanut-specific immunoglobulin E (IgE) and immunoglobulin G4 (IgG4), changes in skin prick test (SPT) mean wheal diameters will also be assessed.
- Physician global assessment: Disease activity as measured on a 100 mm visual analogue scale (VAS)

3.7 Exploratory Endpoint

- The proportion of subjects who tolerate an OFC to a cumulative dose of 4043 mg of peanut protein with no more than mild symptoms

4. Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

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

1. Completion of study ARC001
2. Written informed consent from subject and/or parent/guardian
3. Written assent from all subjects as appropriate
4. Use of birth control for females of child-bearing potential
5. No change in the status of any longitudinally applicable ARC001 inclusion criteria

4.2 Exclusion Criteria

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

1. Early termination from ARC001
2. For former active AR101 (CPNA) treatment subjects from ARC001 (Group 2), failure to tolerate with no or mild symptoms 300 mg of peanut protein in their ARC001 exit DBPCFC
3. Pregnancy or lactation
4. For former placebo subjects from ARC001 (Group 1), a lapse in dosing of more than 10 days from completion of ARC001
5. Change in the status of any longitudinally applicable ARC001 exclusion criteria

4.3 Premature Subject Termination from the Study

4.3.1 Criteria

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

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

1. Life-threatening symptoms (CoFAR Grade 4; refer to **Appendix 4 Table A4-3**), 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 **Appendix 4 Table A4-3**), 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
3. Poor control or persistent activation of secondary atopic disease (e.g., atopic dermatitis, asthma)
4. Started on angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing doctor
5. Pregnancy
6. Circumstances (e.g., concurrent illness, such as gastroenteritis) requiring missed peanut OIT maintenance dosing of > 14 consecutive days
7. Non-adherence with home peanut OIT dosing protocol (excessive missed days; i.e., > 7 consecutive days, or 3 consecutive days missed on 3 or more occasions within a 9-month period, if doses not held per investigator instruction for treatment of an AE) would be a safety issue warranting discontinuation

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

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

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

4.3.2 Follow-up of Subjects Who Discontinue Treatment

Subjects who prematurely discontinue treatment will be monitored for safety for approximately an additional 14 days from the time of cessation of dosing, if possible, and should return for an Early Termination visit at that time (see **Section 6.3.17**).

5. Study Medication

5.1 Formulation, Packaging and Labeling

The active study product is AR101 [Characterized Peanut Allergen (CPNA)] in the form of peanut flour formulated with a bulking agent and a flow agent in pre-measured graduated doses comprising break-apart capsules containing 0.5, 1.0, 10, 100, and 475 mg each of peanut protein for administering doses of up to 2000 mg, inclusive. For doses ≥ 1000 mg, and for 300 mg dosing during the Extended Maintenance Phase, AR101 (CPNA) may alternatively be provided in foil sachets during the High-dose Buildup and Extended Maintenance Phases. Study product is characterized with a high performance liquid chromatography (HPLC) fingerprint and specific enzyme-linked immunosorbent assays (ELISAs) performed against key allergenic proteins to demonstrate stability and lot-to-lot comparability.

All study products will be packaged and labeled at the central manufacturer. The products will then be shipped to a drug depot where they will be labeled and inventoried for shipment to the clinical sites. Study products will be shipped by the drug depot to the site pharmacist for distribution to the site study personnel. A clinical site pharmacist will dispense study products to the investigational site staff in a manner consistent with the current dose level.

All study products will be stored in a secure location and kept refrigerated between 2°C and 8°C.

5.2 Preparation, Administration, and Dosage

The pre-packaged study product will be provided from the site pharmacy in appropriate doses to deliver the specified dose as outlined in **Section 3**. The capsules should be drawn apart, and gently rolled between finger and thumb, followed by a light tap to ensure full delivery of

contents. Sachets should be gently opened while holding the sachet over the container of vehicle food. The contents of the capsules or sachets are to be thoroughly mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other age-appropriate food. The food may not be heated before consumption, and must also be one to which the subject is not additionally allergic. The product must be consumed promptly after mixing. If there is a delay of more than 24 h prior to consumption, the product will be discarded and a new product dose mixed and consumed. Every attempt will be made to administer the dose of study product at the same time of day. A target interval of at least 12 h should pass between doses.

The pharmacist will prepare the capsules or sachets according to the specified dose per subject. The subject or supervising adult will thoroughly mix the provided capsule or sachet contents with the vehicle food.

Subjects will receive at their clinic visits a set of capsules to be taken at home according to their specific dose level. The subjects should be instructed to document capsules and sachets taken at home using diary logs and bring all unused capsules and sachets back to the clinic at every visit.

Subjects should withhold their daily home dose on an in-clinic dosing day but should take all other prescribed medications. Note that the daily home dose should be taken as part of a meal. It is recommended that the dose be taken at a consistent time (within a 4-hour time period), and it is critical to take the dose every day. Doses should be separated by at least 12 h.

5.3 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) 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 drug dispensed.

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

5.4 Assessment of Compliance with Study Treatment and Monitoring

The subject or subject's family will document daily dosing and any reaction to at-home dosing on diary logs. Central monitoring of compliance will be performed. Subjects/families will be provided with 24-h emergency contact information for their site.

All unused study medication and diary logs should be brought back to the clinic with each visit for reconciliation of remaining capsules.

5.5 Modification of Study Treatment

As described in the protocol (**Section 6.6**), peanut OIT doses may be adjusted by the study physician if the subject is unable to tolerate their scheduled dose. If such a dose modification

occurs, the subject will return all unused capsules or sachets of study medication during a dose adjustment visit, and be dispensed new capsules at the adjusted dose level.

5.6 Concomitant Medications

Except as indicated in **Section 5.9**, all subjects may continue their usual medications, including those taken for asthma, allergic rhinitis, and atopic dermatitis, during the study. However, they must be able to discontinue antihistamines 5 half-lives prior to the initial day of escalation, skin prick testing, and oral food challenges. Usual topical steroid use is permitted at the time of skin prick testing.

5.7 Prophylactic Medications

None.

5.8 Rescue Medications

Treatment of individual allergic reactions during peanut OIT should be with either an antihistamine and/or epinephrine, along with IV fluids, albuterol, oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely already to have an epinephrine auto-injection device, but for those who do not, an epinephrine auto-injection device will be provided. Subjects and parents will be trained in proper use and will be able to demonstrate proper technique with the epinephrine auto-injection device.

5.9 Prohibited Medications

1. Omalizumab (Xolair)
2. Systemic (oral) 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
3. Beta-blockers (oral)
4. Angiotensin-converting enzyme (ACE) inhibitors
5. Angiotensin-receptor blockers (ARB)
6. Calcium channel blockers

6. Study Procedures

6.1 Enrollment and Randomization

At the Exit Visit for ARC001, subjects who have successfully completed the ARC001 study, signed ARC002 informed consent (and assent, as age-appropriate), and satisfied all ARC002 inclusion/exclusion criteria will be enrolled into ARC002. Subjects will be unblinded to their ARC001 treatment assignment and their treatment assignment will be verified against the ARC001 unblinded site pharmacist's records prior to enrollment in ARC002. Subjects will be assigned to Group 1 or Group 2 on the basis of their treatment assignment in ARC001without re-randomization; Group 1 comprising those subjects who were assigned to placebo in ARC001; and Group 2 comprising those subjects who were assigned to active AR101 (CPNA) treatment in ARC001.

Subjects in Group 1, formerly receiving placebo in ARC001, should begin dosing in ARC002 within 5-10 days of completion of ARC001, and must return to the CRC within 5-10 days of ARC001 if they are participating in the ITN/Benaroya Optional Blood draws.

6.2 Rollover Visit (Group 1 and Group 2)

All screening procedures for the ARC002 study will be performed during the ARC001 Exit Visit. Screening should be performed in a single day and will include the following procedures:

- Informed consent and assent
- Confirming treatment assignment from ARC001
- Inclusion/exclusion criteria review
- Interval medical, allergy, and dietary history
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure [BP], pulse rate [PR], body temperature)
- Peak Expiratory Flow Rate (PEFR) prior to any DBPCFC; 3 attempts of PEFR are to be performed, and the best value taken. PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic blood draw), the amount to be specified by local laboratory guidelines
- Optional blood draw for exploratory analysis by ITN/Benaroya. Blood draw should only be performed in children weighing ≥ 30 kg. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml. Blood draw should be collected per National Institutes of Health (NIH) guidelines.
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS

6.2.1 Optional ITN/Benaroya Blood Draw Visit (Group 2 only)

Group 2 subjects who have consented to the Immune Tolerance Network (ITN)/Benaroya optional blood draw, will return to the CRC 5-10 days following the ARC001 Exit/ARC002 Rollover Visit. The following will be performed:

- Optional blood draw for exploratory analysis by ITN/Benaroya. Blood draw should only be performed in children weighing ≥ 30 kg. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml. Blood draw should be collected per National Institutes of Health (NIH) guidelines.

6.3 Study Treatment Visits

A physician will be available at all times during study visits. See **Section 6.10** for visit windows.

6.3.1 Group 1 only: Initial Escalation Phase, Days 1 to 3

The Initial Escalation Phase Visit for Group 1 subjects will occur 5 to 10 days after the ARC001 Exit/ARC002 Rollover Visit. The following assessments will be performed for the Initial Escalation Phase at the Clinical Research Center (CRC):

Day 1 Initial Escalation:

- Diet history
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Optional blood draw for exploratory analysis by the Immune Tolerance Network (ITN)/Benaroya. Blood draw should only be performed in children weighing ≥ 30 kg. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml. Blood draw should be collected per National Institutes of Health (NIH) guidelines.
- OIT administration of AR101 (CPNA) with dosing beginning at 0.5 mg and followed by graduated doses up to 6 mg (if tolerated). Subjects tolerating less than 3 mg single-dose at the end of Day 1 will be considered an initial day escalation failure. The schedule for Day 1 dose escalation is shown in **Table 3-1**.
- Monitoring for allergic symptoms (see **Section 6.6**)
- Adverse events monitoring

Subjects may have clear liquids or JELL-O during the Day 1 Initial Escalation while they are being given the desensitization doses.

If symptoms occur which prevent escalation to 6 mg, the highest tolerated dose (at least 3 mg) will be accepted as the "desensitization" dose for further escalation (see **Figure 6-2**). The maximum tolerated dose on Day 1 (i.e., 3 or 6 mg) will be given on Day 2 as a single dose under medical observation at the CRC. If moderate symptoms occur on Day 2, the subject will return to the CRC on Day 3 for the next lower dose (must be at least 3 mg) under direct observation. If symptoms prevent initial escalation desensitization dosing to 3 mg, the subject will be dropped from study treatment due to escalation failure and followed longitudinally for safety. These subjects will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

Day 2 Initial Escalation:

All subjects will return to the clinic on Day 2 for their next dose. This dose will be the previous day's dose or the last tolerated dose from the initial day escalation. The maximum dose is 6.0 mg. The minimum dose for Day 2 is 3.0 mg.

Those subjects administered 3.0 mg:

- If tolerated on Day 2, return home on that dose for 2 weeks until the next escalation.
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms
- If not tolerated, the subject is considered an escalation failure and will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.16**).

Those subjects administered 6.0 mg:

- If tolerated, return home on that dose for 2 weeks until next escalation
- If not tolerated, return on Day 3 with a 1-step reduction (3.0 mg)

Day 3 Initial Escalation:

Those subjects with moderate symptoms on Day 2 at the 6.0 mg dose will return on Day 3 for an observed dose. The maximum dose on Day 3 would be 3.0 mg.

Those subjects administered 3.0 mg

- If tolerated, return home on that dose for 2 weeks until next escalation.
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms
- If not tolerated, the subject is considered an escalation failure and will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.16**).

6.3.2 Group 1 only: Low-dose Buildup Phase Up-dosing Visits

The following procedures are scheduled for the Low-dose Buildup Phase Visits, which will occur every 2 weeks for approximately 6 months (20 to 36 weeks):

- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Up-dosing (bi-weekly) under observation at the clinic to a maximum of 300 mg daily dose. (Subjects should not take their daily maintenance dose on the day of clinic visits).
- Dose assessment to determine whether to maintain the subject at the current dose or to up-dose to the next level
- Take home capsules for daily dosing until next visit

- Return unused capsules to the clinic at each visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

Subjects who require dose reduction during a 2-week period will reset their 2-week escalation schedule to maintain the new dose for a 2-week period prior to attempting to escalate again. The procedure for setting the new, lower, dose is outlined in **Section 6.6** and depends on the severity of the dose-related symptoms. Dose escalation attempts may be postponed for 1-2 extra weeks based on clinical judgment. An escalation attempt must be made within 4 weeks, unless escalation is to be delayed further due to administration of epinephrine as defined in **Section 6.6**. Failure to successfully escalate for three consecutive attempts will result in the subject being considered an escalation failure, at which point the subject will be dropped from study treatment and followed longitudinally for safety. Subjects who fail escalation will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

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

6.3.3 Group 1 only: Month 3 Low-dose Buildup Phase Visit

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Study product administration at clinic
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

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

6.3.4 Group 1 only: End of Low-dose Buildup Phase Visit

Group 1 subjects who tolerate a daily dose of 300 mg peanut protein by Week 34, and who are maintained at this dose for 2 weeks, will undergo a post-Low-dose Buildup Phase Visit (approximately 6 months post-Initial Escalation Phase).

Group 1 subjects who fail to reach a dose of 300 mg/d peanut protein will be considered escalation failures and discontinued from the study. They will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

The following procedures will be performed at the End of Low-dose Buildup Phase Visit:

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic blood draw), the amount to be specified by local laboratory guidelines.
- Optional blood draw (pre-DBPCFC) for exploratory analysis by the Immune Tolerance Network (ITN)/Benaroya. Blood draw should only be performed in children weighing ≥ 30 kg. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml. Blood draw should be collected per National Institutes of Health (NIH) guidelines. (See **Section 6.1** and **Appendix 1-A** Schedule of Events)
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS
- Post-Low-dose Buildup Phase DBPCFC
- Return any unused capsules to the clinic
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

Subjects who fail to tolerate the post-Low-dose Buildup Phase DBPCFC at ≥ 300 mg will be considered escalation failures and will be discontinued from the study for safety considerations.

They will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

Those subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein, will enter the ~3-month Plateau Phase of continued dosing at 300 mg/d. They will receive capsules for daily home dosing of 300 mg until the next visit.

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

6.3.5 Group 2 only: Plateau Phase Initiation Visit

For Group 2 subjects, the Plateau Phase will be initiated during the ARC001 Exit / ARC002 Rollover Visit. The following will occur for the Group 2 subjects at this visit:

- Take home capsules for daily dosing of 300 mg until the next visit
- Monitoring for allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

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

6.3.6 All Subjects (Groups 1 and 2): Plateau Phase Visits

Plateau Phase Visits will occur approximately every 4 weeks.

The following procedures will be performed:

- Medical/allergy history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Study product administration at clinic
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

In the event that one or two episodes of dose reduction from the stable dose of 300 mg/d are required during the Plateau Phase, the Plateau Phase may be extended up to an additional 12 weeks (to a maximum of 24 weeks) on an individual basis. Temporary dose reductions instituted at the investigator's discretion, while a subject is suffering from symptoms of an upper respiratory infection or influenza, or during menses (see **Section 6.6.2**, will count as one of the two allowable dose reduction episodes, if the reduced dose is maintained for > 3 days (in which case the subject is to maintain the new, reduced dose for 2 weeks before re-escalating biweekly in a stepwise fashion).

Dosing will be discontinued during the Plateau Phase for any of the following reasons:

- Requiring more than two episodes of dose reduction from a stable dose of 300 mg/d (dose adjustments within the first 3 days of a dose reduction do not constitute separate episodes of dose reduction)
- Following a dose reduction, failure to re-escalate after 3 attempts
- Inability to maintain a dose of 300 mg/d for at least the last 4 consecutive weeks of the Plateau Phase.

If dosing is discontinued, the subject will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

The procedures for escalating back up to a dose of 300 mg/d following a dose reduction in the Plateau Phase will follow the same re-escalation rules as for the Buildup Phases.

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

6.3.7 All Subjects (Groups 1 and 2): End of Plateau Phase Visit

Subjects who successfully complete the Plateau Phase (having tolerated 300 mg/d continuously for the last 4 weeks of the Plateau Phase, and having had no more than two dose reduction episodes during the phase), will return to the clinic for the End of Plateau Phase Visit. This visit should occur approximately 3 months after (and no later than 6 months after) the Plateau Phase Initiation Visit.

Subjects who are unable to tolerate daily dosing at 300 mg (as defined above) will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

The following procedures will be performed at the End of Plateau Phase Visit:

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)

- PEFR (3 attempts are to be performed, and the best value taken)
- Urine pregnancy test, for females of childbearing potential
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic blood draw), the amount to be specified by local laboratory guidelines.
- Optional blood draw (pre-DBPCFC) for exploratory analysis by the ITN/Benaroya. Blood draw should only be performed in children weighing ≥ 30 kg. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml. Blood draw should be collected per National Institutes of Health (NIH) guidelines.
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS
- Post-Plateau Phase DBPCFC
- Return any unused capsules to the clinic
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

Subjects who fail to tolerate the post-Plateau Phase DBPCFC at ≥ 300 mg, after not more than 2 attempts (refer to **Section 3.2.5**), will be discontinued from the study for safety considerations. They will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

Subjects who tolerate the DBPCFC at ≥ 300 mg of peanut protein, will be given the option to enter the Optional High-dose Buildup Phase. Supplemental informed consent must be obtained prior to entry into the Optional High-dose Buildup Phase.

Subjects who consent to the Optional High-dose Buildup Phase will return to the clinic on the next day for the Optional High-dose Buildup Phase Initiation Visit. Subjects who do not consent will enter directly into the Extended Maintenance Phase.

All subjects will continue to follow a peanut-avoidant diet for the duration of the study.

6.3.8 All Subjects (Groups 1 and 2): Optional High-dose Buildup Phase Initiation Visit

The Optional High-dose Buildup Phase Initiation Visit is to occur on the day following the post-Plateau Phase DBPCFC (End of Plateau Phase Visit). The visit is intended to confirm the safety of the starting dose for the Optional High-dose Buildup Phase. Based on the outcome of the post-Plateau Phase DBPCFC, subjects will target a starting dose for the Optional High-dose Buildup Phase of either 400 mg, 575 mg, or 950 mg (see **Figure 6-1**).

If the target starting dose for the Optional High-dose Buildup Phase is tolerated, subjects will continue daily home dosing at that dose level and undergo dose-escalation at their biweekly CRC visits according to the Optional High-dose Buildup Phase schedule (**Table 3-3**).

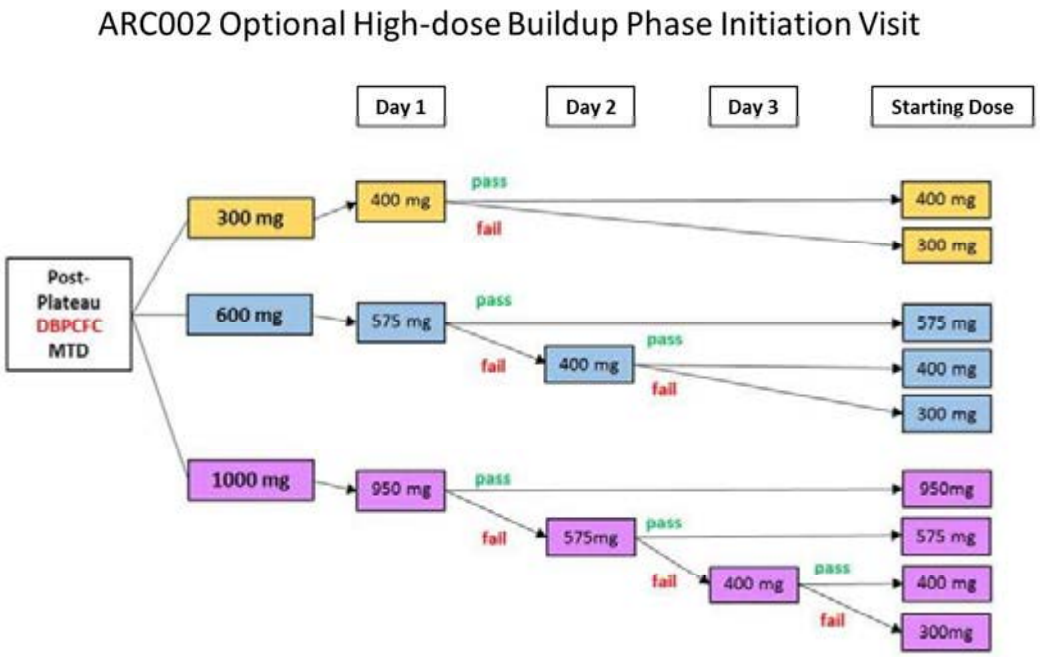
If the target starting dose for the Optional High-dose Buildup Phase is not tolerated, subjects may return to the CRC for up to 2 additional consecutive days to establish the appropriate dose level for starting their individual high-dose buildup.

Testing of the target starting doses and assignment of the subsequent dosing levels is to proceed as follows:

- Subjects whose highest tolerated dose in the post-Plateau Phase DBPCFC was 300 mg will escalate to a dose of 400 mg of peanut protein as AR101 (CPNA) in the CRC.
  - Those subjects who tolerate the 400 mg dose will receive capsules and instructions for daily dosing of 400 mg.
  - Those subjects who fail to tolerate the 400 mg dose are to continue home dosing at the 300 mg/d dose and may attempt dose escalation according to the Optional High-dose Buildup Phase schedule (**Table 3-3**) at the next biweekly visit.
- Subjects whose highest tolerated dose in the post-Plateau Phase DBPCFC was 600 mg will confirm tolerability at a 575 mg dose of peanut protein as AR101 (CPNA) in the CRC.
  - Those subjects who are confirmed to tolerate a 575 mg dose will receive capsules and instructions for daily dosing of 575 mg.
  - Those subjects who fail to tolerate the 575 mg dose may return to the CRC the following day (Day 2) to be tested with a 400 mg dose. If tolerated, the subject will receive capsules and instructions for daily dosing of 400 mg; if not tolerated, the subject is to continue home dosing at the 300 mg/d dose. In either case, dose escalation may be attempted according to the Optional High-dose Buildup Phase schedule (**Table 3-3**) at the next biweekly visit.
- Subjects whose highest tolerated dose in the post-Plateau Phase DBPCFC was 1000 mg will confirm tolerability at a 950 mg dose of peanut protein as AR101 (CPNA) in the CRC.
  - Those subjects who are confirmed to tolerate a 950 mg dose mg will receive capsules and instructions for daily dosing of 950 mg.
  - Those subjects who fail to tolerate the 950 mg dose may return to the CRC the following day (Day 2) to be tested with a 575 mg dose. If tolerated, the subject will receive capsules and instructions for daily dosing of 575 mg; if not tolerated, the subject may return to the CRC the following day (Day 3) to be tested with a 400 mg dose. If the 400 mg dose is tolerated, the subject will receive capsules and instructions for daily dosing of 400 mg; if not tolerated, the subject is to continue home dosing at the 300 mg/d dose. In any case, dose escalation may be attempted

according to the Optional High-dose Buildup schedule (**Table 3-3**) at the next biweekly visit.

Figure 6-1: Optional High-dose Buildup Phase Initiation Visit



The following procedures are scheduled for the Optional High-dose Buildup Phase Initiation Visit:

- Supplemental informed consent
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken)
- Administer in the CRC the dose of peanut protein, in the form of AR101 (CPNA), appropriate for the highest tolerated dose from the previous day's DBPCFC, as illustrated in **Figure 6-1**
- Observe for 30 min. If the subject exhibits mild symptoms, the duration of the observation period should be 1-2 h. For moderate to severe symptoms, the observation period should be at least 4 h and up to 24 h based on symptoms and the treatment regimen needed to stabilize the subject's condition.
- Return any unused capsules to the clinic
- Take home capsules for daily dosing until next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

6.3.9 All Subjects (Groups 1 and 2): Optional High-dose Buildup Phase Up-dosing Visits

The Optional High-dose Buildup Phase will last for approximately 10 to 30 weeks with subjects returning to the CRC every 2 weeks for up-dosing to a target maximum of 2000 mg/d. Subjects will proceed with dose escalation according to the Optional High-dose Buildup Schedule (**Table 3-3**), continuing on from the point at which they entered the schedule. Subjects should not take their daily maintenance dose on the day of clinic visit.

The following procedures are scheduled for the Optional High-dose Buildup Phase Up-dosing Visits:

- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Study product administration at clinic
- Dose assessment to determine whether to maintain the subject at the current dose or to up-dose to the next level
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

Subjects who require dose reduction during the 2-week period will reset their 2-week escalation schedule to maintain the new dose for a 2-week period prior to attempting to escalate again. Any dose escalation attempts may be postponed for 1-2 extra weeks based on clinical judgment. If escalation is not successful by 4 weeks, the dose level that is tolerated will be considered the maximum tolerated dose (MTD); escalation will be delayed further in the event that epinephrine had been administered, as defined in **Section 6.6**.

Subjects who fail to successfully re-escalate for three consecutive attempts should end the Optional High-dose Buildup Phase and enter the Extended Maintenance Phase; the tolerated dose level should be maintained as the new MTD for the duration of the Extended Maintenance Phase. The exception to this is if, after three consecutive attempts, the subject is unable to re-escalate to a minimum dose of 300 mg/d, the subject should be considered unable to tolerate 300 mg of peanut protein as AR101 (CPNA) , discontinued from the study, and asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

Subjects who reach their MTD before reaching the target 2000 mg/d dose will enter the Extended Maintenance Phase at their next visit, i.e., 2 weeks after the last (failed) in-clinic dose-escalation attempt.

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

6.3.10 All Subjects (Groups 1 and 2): Month 3 Optional High-dose Buildup Phase Visit

For subjects who have not transitioned to the Extended Maintenance Phase within 3 months of the Optional High-dose Buildup Phase Initiation Visit, a Month 3 Optional High-dose Buildup Phase Visit will be conducted (to coincide with the scheduled bi-weekly up-dosing visit). Subjects should not take their daily maintenance dose on the day of clinic visit.

The following procedures will be performed:

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Study product administration at clinic
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

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

6.3.11 All Subjects (Groups 1 and 2): End of Optional High-dose Buildup Phase Visit

Subjects must maintain dosing at 2000 mg/day (or their MTD) for two consecutive weeks before completing the End of Optional High-dose Buildup Phase Visit. This visit will also serve as the Initiation Visit for the Extended Maintenance Phase. Subjects should not take their daily maintenance dose on the day of clinic visit.

The following procedures will be performed at this visit:

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic blood draw), the amount to be specified by local laboratory guidelines.
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS
- Study product administration at clinic
- Return any unused capsules to the clinic
- Take home capsules for daily dosing at MTD until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

Note: DBPCFCs will not be performed at the conclusion of the Optional High-dose Buildup Phase.

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

6.3.12 All Subjects (Groups 1 and 2): Week 2 Extended Maintenance Phase Visit

Subjects should not take their daily maintenance dose on the day of clinic visit.

The following procedures will be performed at this visit:

- Medical/allergy history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken)
- Study product administration at clinic

- Return unused drug supply to the clinic
- Take home capsules for daily dosing at MTD until the next visit
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- Telephone follow-up one week after visit to monitor dosing compliance and allergic symptoms

For any noted symptoms during the Extended Maintenance Phase, it is advised that, in general, the same study dosing rules be followed as for the Low-dose Buildup and Optional High-dose Buildup Phases. Subjects who require dose reduction during the Extended Maintenance Phase should maintain the new dose for a 2-week period prior to attempting to escalate again. Any dose re-escalation attempts may be postponed for 1-2 extra weeks based on clinical judgment. A re-escalation attempt should be made by 4 weeks, unless escalation is to be delayed further as a consequence of epinephrine having been administered, as defined in **Section 6.6**. Failure to successfully re-escalate for three consecutive attempts should result in the tolerated dose level being maintained as the new MTD for the duration of the Extended Maintenance Phase. The exception to this is if, after three consecutive attempts, the subject is unable to re-escalate to a minimum dose of 300 mg/d, the subject should be considered unable to tolerate 300 mg/d of peanut protein as AR101 (CPNA), discontinued from the study and asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

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

6.3.13 All Subjects (Groups 1 and 2): Week 6 Extended Maintenance Phase Visit

- Same procedures as for the Week 2 Extended Maintenance Phase Visit

6.3.14 All Subjects (Groups 1 and 2): Week 12 Extended Maintenance Phase Visit

Same procedures as for the Week 2 Extended Maintenance Phase Visit.

The following procedures should be performed prior to study product administration at clinic:

- Blood draw for peanut-specific IgE and IgG4 measurement, the amount to be specified by local laboratory guidelines
- Skin prick test to peanut extract
- Urine pregnancy test, for females of childbearing potential

6.3.15 All Subjects (Groups 1 and 2): Q 3 Month (Every 3 Months) Extended Maintenance Phase Visits

Visits to occur at Week 24, 36, 48, and so on for the Extended Maintenance Phase until the study exit visit.

Note: Starting with the first of the Q 3 Month Visits (Week 24), the permissible window around study visits will be extended to 1 week. The amount of study product, AR101 (CPNA), supply taken home for daily dosing should be sufficient to accommodate this window.

- Same procedures as for the Week 12 Extended Maintenance Phase Visit
- Urine pregnancy test, for females of childbearing potential

Note: Starting with the Week 36 Q 3 Month Visit, skin prick testing to peanut extract and blood draw for peanut-specific IgE and IgG4 measurement (the amount to be specified by local laboratory guidelines) will be conducted on alternate Q 3 Month Visits. The alternate-visit sequence for SPT and IgE/IgG4 blood draws will start by withholding these tests on Week 36 of the Extended Maintenance Phase and performing them on Week 48 of the Extended Maintenance Phase, i.e., SPT and IgE/IgG4 blood draws will be performed at Week 24, Week 48, Week 72, etc.

6.3.16 All Subjects (Groups 1 and 2): Study Exit Visit and Optional Open-label Food Challenge

This study will be terminated in accordance with Protocol Amendment 3. Upon IRB approval of Protocol ARC008 and at the time of IRB approval of Protocol Amendment 3 at the study site, all subjects remaining on study will be asked to return to the study center to complete the Study Exit visit where they will have the option to undergo an Open-Label Food Challenge (OFC) to a maximum cumulative dose of 4043 mg of peanut protein. If the subject consents to have an end of study OFC, the end of study procedures will be accomplished in one day in clinic. Some exit questionnaire interviews may be conducted afterwards via telephone or web conferencing.

Subjects who do not consent to this end of study OFC will complete the study after undergoing the procedures listed in the Early Termination / Exit Visit (see **Section 6.3.17**).

Regardless of completion of the exit OFC, subjects will be offered continued treatment in a rollover trial ARC008 upon exit from this study.

For subjects who consent to participate in the optional OFC, the following procedures* will be performed at the CRC:

- Sign ARC002 updated Informed consent and assent
- Medical/allergy history
- Skin prick test to peanut extract
- Blood draw for peanut-specific IgE and IgG4 measurement, the amount to be specified by local laboratory guidelines
- Diet history
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)

- PEFR (3 attempts are to be performed, and the best value taken).
- Urine pregnancy test, for females of childbearing potential
- Physician global assessment of disease activity using a 100-mm VAS
- Return any unused capsules or sachets to the clinic
- Monitoring for compliance and allergic symptoms
- OFC with up to 4043 mg peanut protein (cumulative).
- Monitoring for allergic symptoms (see **Section 6.6**)
- Adverse events monitoring
- EQ-5D-5L Questionnaire* (by telephone or web conference)
- TSQM-9 Questionnaire
- Parent/Patient Exit Survey
- Optional Peanut Allergy Telephone/Web-based Interview*

At the completion of all in-clinic Study Exit visit study procedures, each subject will be offered the option to enroll into the ARC008 study to permit continued treatment with AR101.

- Sign informed consent and assent for ARC008 if rolling over

*These procedures may occur in-clinic during the Study Exit Visit, or at home shortly after the Study Exit Visit.

6.3.17 Early Termination / Exit Visit

Subjects who discontinue the study prematurely for any reason, including inability to tolerate a dose of 300 mg/d of peanut protein during a DBPCFC,should undergo an Early Termination Visit. For subjects discontinuing prematurely and not planning on continuing AR101 treatment in ARC008, the visit is to occur 14 days (minus 3 days to plus 7 days) from the last dose of AR101 (CPNA). Those subjects who do not consent to participate in the optional OFC at the end of study will undergo the following Exit procedures* in clinic. Some exit questionnaire interviews may be conducted afterwards via telephone or web conferencing.

Early Termination / Exit Visit procedures are as follows:

- Medical/allergy history
- Diet history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken)
- Urine pregnancy test, for females of childbearing potential

- Blood draw for peanut-specific IgE and IgG4 measurement, the amount to be specified by local laboratory guidelines.
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS
- Return any unused capsules or sachets to the clinic
- Monitoring for compliance and allergic symptoms
- Adverse events monitoring
- EQ-5D-5L Questionnaire* (by telephone or web conference)
- TSQM-9 Questionnaire
- Parent/Patient Exit Survey
- Optional Peanut Allergy Telephone/Web-based Interview*

*These procedures may occur in-clinic during the Early Termination/Exit Visit, or at home shortly after the Early Termination/Study Exit Visit.

6.4 Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) in accordance with PRACTALL guidelines

All DBPCFCs are to be performed in accordance with PRACTALL guidelines[24] by feeding gradually increasing amounts of peanut flour or placebo, at 20-30 min intervals, under physician observation. The DBPCFCs are to be conducted as 2 challenges during a single-day visit or over 2 days, using placebo for one challenge and peanut flour for the other. If conducted in a single day, at least 3 h must separate the first half of the challenge from the second half of the challenge. The challenge is performed under double-blind conditions so that neither the subject, nor the subject's caregiver nor the physician knows which challenge contains the peanut or the placebo.

6.4.1 Group 1 only: Post-Low-dose Buildup Phase Double-Blind, Placebo-Controlled Food Challenge (DBPCFC)

The post-Low-dose Buildup Phase DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in an unaltered sequence without repeating any dose. The procedure will also be modified in that the top dose will be capped at 600 mg (1043 mg cumulative) peanut protein or placebo. The doses shown in **Table 6-1**, and the PRACTALL rules for safety, assessment, scoring, and stopping will be used.

Table 6-1: Post-Low-dose Buildup Phase DBPCFC doses using peanut flour with 50% peanut protein content for Group 1

Challenge Doses		
Peanut protein (mg)	**Peanut flour with 50% protein content (mg)**	**Cumulative Dose (mg)**
3	6	3
10	20	13
30	60	43
100	200	143
300	600	443
600	1200	1043

6.4.2 All Subjects (Group 1 and 2): Post-Plateau Phase Double-Blind, Placebo Controlled Food Challenge (DBPCFC)

The post-Plateau Phase DBPCFC will be conducted in the same manner as the previous DBPCFC, but with a top dose of 1000 mg (2043 mg cumulative) peanut protein added, as shown in **Table 6-2**. The optional Exit Visit OFC will be conducted with peanut protein provided by Aimmune, using a top dose of 2000 mg (4043 mg cumulative) peanut protein added, as shown in **Table 6-3**.

Table 6-2: Post-Plateau Phase DBPCFC doses using peanut flour with 50% peanut protein content

Challenge Doses		
Peanut protein (mg)	**Peanut flour with 50% protein content (mg)**	**Cumulative Dose (mg)**
3	6	3
10	20	13
30	60	43
100	200	143
300	600	443
600	1200	1043
1000	2000	2043

Table 6-3: Exit OFC doses using peanut food challenge material

Peanut protein (mg)	Cumulative Dose (mg)
3	3
10	13
30	43
100	143
300	443
600	1043
1000	2043
2000	4043

6.5 Other Assessments

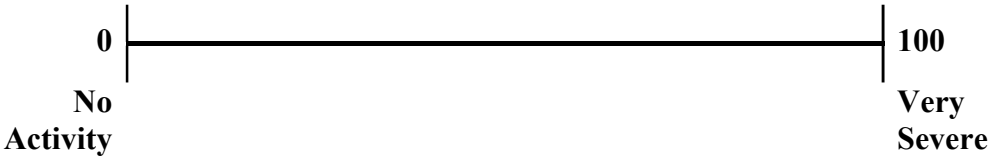
6.5.1 Physician Global Assessment

A 100-mm visual analog scale (VAS) will be used by the investigators to assess overall disease activity as a marker for safety.

In assessing overall disease activity, the investigator should consider the frequency of allergic reactions (both observed and reported), their type, their severity, and the dose level at which they have occurred. With these factors in mind, the investigator is to assign a single integrated overall disease activity score.

The investigators will be asked:

"How would you rate the severity of the overall disease activity on a scale of 0, no disease activity, to 100, very severe disease activity?"



Investigators are permitted to refer back to previous assessments when making their VAS determination of overall disease activity.

Although not validated specifically as an instrument for evaluating food allergies, the VAS is, nevertheless, a widely used tool in assessing disease activity, especially in inflammatory diseases.

6.5.2 Exit Assessments

All subjects will be asked to complete the following questionnaires at the end of the study.

- EQ-5D-5L[31] – a standardized preference-based measure of health status

- TSQM – 9 – an abbreviated treatment satisfaction questionnaire for medication (**Appendix 6**)
- Parent-Completed (**Appendix 7**) and Patient-Completed (**Appendix 8**) Exit Surveys designed to examine parent's/caregiver's and patient's experiences and satisfaction with the study drug

In addition, subjects will also be asked to complete an optional peanut allergy interview (**Appendix 9**) to assess subjects' peanut allergies, how peanut allergy impacted subjects before oral immunotherapy, and the impact of and changes in peanut allergy following oral immunotherapy. The interview will also assess subjects' experience taking the oral immunotherapy and any positive or negative aspects of the treatment of importance to the subjects. The information will be gathered to better understand the impacts of peanut allergy on subjects' lives and what improvements or changes are most meaningful and important to allergy sufferers.

The TSQM-9 and the and the Parent-Completed and Patient-Completed Exit Surveys will be administered at the study exit visit. The EQ-5D-5L and the optional peanut allergy interview to assess subjects' peanut allergies will be conducted by telephone interview following subjects' completion of the study.

6.6 Reactions and Treatment of Reactions

6.6.1 Reactions and Treatment of Reactions to Peanut OIT during Initial Escalation Phase (Group 1)

The process algorithm for symptoms during the Initial Escalation Phase is shown in **Figure 6-2.**

Subjects may develop symptoms during the Initial Escalation Phase, similar to those seen during other desensitization protocols (e.g., venom immunotherapy, drug desensitization). The severity of the reaction will be determined on the basis of the investigator's judgment, using the definitions in the PRACTALL consensus report on DBPCFC as a general guide. The investigator's judgment will also be required to determine the best course of action, with possible actions being the following:

- Extension of time interval between dosing (up to a total of 60 min) without any additional treatment
- Institution of 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 min of last dose, if assessed as safe
- Treating additionally with beta-agonist nebulizer, epinephrine, oxygen, IV fluids, and/or glucocorticosteroids, and discontinuing dose-escalation
- Discontinuation of desensitization protocol

For *oral/pharyngeal pruritus* occurring in isolation – the recommended action is to continue the normal dosing in 30 min (though the action taken is, as always, at the investigator's clinical discretion).

For *mild symptoms*, including, but not limited to:

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

Depending on the investigator's discretion, the action should be either:

- Advance to next dose in 30–60 min *or*
- Treat with antihistamine and then resume dose escalation within 60 min of last dose, if symptoms have resolved to the point where the investigator assesses the subject as safe to continue dosing (i.e., having no or minimal residual signs or symptoms)

If *moderate symptoms* occur, including, but not limited to:

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

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

If moderate symptoms occur at any of the doses below 6 mg (i.e., up to and including 3 mg), then the desensitization protocol will be discontinued and the subject considered an escalation failure. The decision to discontinue escalation (at any dose below, or at, 3 mg) is based solely on the determination that the symptoms of allergic reaction are moderate, regardless of whether the treatment is instituted or what type of treatment is instituted. If moderate symptoms occur only at the 6 mg dose, then the following day's dose (Day 2 or Day 3) will be reduced to 3 mg.

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

If more *severe symptoms* occur, including, but not limited to:

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

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

Summary of Initial Escalation Phase (Group 1 only) Dosing Requirements (see also **Figure 6-2**):

In general, if the subject requires one or two doses of antihistamine treatment for mild symptoms during the initial escalation protocol, then the initial escalation may be continued. If, however, the subject requires a second medication (e.g., epinephrine, a beta-agonist, or other medications) in addition to an antihistamine, or more than 2 doses of antihistamines, the initial escalation is to be terminated and the subject will receive no further OIT, even if symptoms are assessed to be mild.

In the event of moderate symptoms occurring during the initial escalation, the initial escalation is to be terminated and the subject will receive no further OIT, regardless of whether treatment is instituted or what type of treatment is instituted. The only exception to this is if the occurrence of moderate symptoms is restricted to the 6 mg dose. In this case, and this case only, may testing be attempted the following day (Day 2 or Day 3) at a reduced dose (3 mg).

If the initial escalation is completed with no symptoms or only mild symptoms, subjects should have, at a minimum, a 2-h post-dosing observation period before continuing in the study. If the subject experiences moderate to severe symptoms, the observation period is to be at least 4 h, and up to 24 h (in an appropriate facility), based on the nature and severity of the symptoms and the treatment regimen required to stabilize the subject's condition.

6.6.2 Reactions to Peanut OIT during Buildup Phases: Preventative and Non-pharmacological Interventions

The process algorithm for symptoms during the buildup/up-dosing phases is shown in **Figure 6-3.**

Subjects will begin their appropriate dosing scheme in the CRC as outlined for either the Low-dose Buildup Phase (Group 1 only) or the Optional High-dose Buildup Phase (both Group 1 and Group 2). Subjects will return for a supervised dose escalation in the clinic every 2 weeks during dose buildup phases. It is advised that CRC staff be in contact with subjects the morning of the day after each dose escalation visit to assess for delayed allergic reactions. Subjects will also be called 1 week after each dose escalation visit to assess for dosing compliance and dose reactions.

With the occurrence of symptoms of a dose-reaction or any allergic reaction, subjects/parents (or guardians) are instructed to call the study site.

Should significant systemic symptoms, which may include mild symptoms based on physician discretion or moderate or greater symptoms, be reported during the daily home dosing, the symptom/dosing algorithm will be followed (see **Figure 6-3**) to determine the best course of action. The appropriate treatment will depend on the type and severity of symptoms.

Subjects will be free from active wheezing or a flare of atopic dermatitis prior to any dose escalation. Subjects will be maintained on their current dose of study product until their flare of asthma or atopic dermatitis resolves.

Subjects will be cautioned against activities likely to increase reactivity (e.g., exercising or taking hot showers or baths within 4 h after dosing).

At the investigator's discretion, temporary dose reductions, ranging from a 1-step decrement (i.e., to the previous dose) to approximately half of the current dose level (to the nearest feasible whole dose), can be instituted while subjects are suffering from symptoms of an upper respiratory infection or influenza, or during menses. If the dose is reduced by more than 1 step or for more than 3 days, the subject is to return to the CRC within 7 days of the dose-reduction for dose re-escalation under direct observation. If the reduction in dose is maintained for ≤ 3 days, then the pre-reduction dose may be resumed directly. For dose reductions of 1 dose level maintained for ≤ 3 days, whether dose re-escalation is to occur at home or in the CRC is at the investigator's discretion. If, however, the reduction in dose is maintained for > 3 days, the subject will reset his or her 2-week escalation schedule to maintain the new dose for a 2-week period prior to re-escalating biweekly in a stepwise fashion.

Doses may also be withheld at the investigator's discretion, in response to an AE, whether the AE is assessed to be treatment-related or not. If doses are withheld for this, or any, reason, the rules for missed peanut OIT doses (**Section 6.7**) apply.

Subjects may develop symptoms during dosing for the buildup phase. The investigator's judgment will be required to determine the best course of action with possible actions being the following:

- Continue with daily home dosing
- Continue the same daily dose for the rest of the 2-week interval, with 50% of the dose split between doses given 8-12 h apart
- Return for repeat dosing in CRC

- Return for dosing of previously tolerated dose (without escalation) in CRC
- Discontinuation of dosing

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

If the subject experiences only oral/pharyngeal pruritus during the administration of the daily dose, then the same dose can be repeated the next day at home and continued throughout the interval unless other symptoms begin to develop (see below).

For *mild symptoms*, defined as:

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

The action should be either to repeat the dose the next day (Day 2) at home or to have the subject return to the CRC the next day (Day 2) for a repeat of the previous day's dose or the last tolerated dose (at the physician's discretion). If the dose is tolerated, then the subject will continue on that dose and return at the normal interval. If the dose causes mild symptoms again, then the subject will return to the CRC (Day 3) and be given the last tolerated dose (i.e., a 1-step dose reduction) or a 2-step dose reduction. If tolerated, the subject will continue on this dose for the normal time interval. If mild symptoms recur, a further 1-2-step reduction should be administered the next day (Day 4). If tolerated then that dose should be continued for 2 weeks. If not tolerated, revert to a lower dose.

If *moderate symptoms* occur, defined as:

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

The action should be to have the subject return to the CRC the next day (Day 2) for dosing with the previous days dose or the last tolerated dose (at the physician's discretion) under observation. If the dose is tolerated, the subject will continue on that daily home dose for the normal time interval per protocol. If the subject does not tolerate this dose, the subject should receive the last tolerated dose or a 1-2 step dose reduction (Day 3) in the CRC or at home if the planned dose

was previously tolerated. If this dose is tolerated, it will be continued as the daily home dose for the normal time interval, then escalation attempted in the CRC as noted below. If this dose is not tolerated, then the next dose will be a 1-2-step reduction in dosing, and the dose will be given in the CRC (Day 4). If this next dose is not tolerated, then a discussion with the Medical Monitor will ensue to make a decision about whether to continue the subject on study-drug treatment in the study.

If more *severe symptoms* occur, defined as:

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

The action should be to treat the subject, and at the physician's discretion either 1) have them return to the CRC the next day (Day 2) for dosing with a 2-step reduction in dose under observation or 2) discontinue them from the active treatment. If the subject tolerates the dose reduction, then they will remain on that dose for 2 weeks and then return to the CRC for the dose escalation. A discussion with the Medical Monitor may ensue to make a decision about whether to continue the subject on active treatment in the study.

If the dose escalation is completed with no symptoms, subjects should be observed for 30 min. If the subject exhibits mild symptoms, the duration of the observation period should be 1-2 h post-protocol. For moderate to severe symptoms, the observation period should be at least 4 h and up to 24 h based on symptoms and the treatment regimen needed to stabilize the subject's condition.

If a subject fails dose escalation after three consecutive attempts (with 2-4 weeks between) during the Low-dose Buildup Phase, he/she will be considered an escalation failure and dosing will be discontinued. The subject will be followed for safety and asked to return to the CRC for an Early Termination Visit 14 days after the last dose.

If a subject fails dose escalation after three consecutive attempts (with 2-4 weeks between) during the High-dose Buildup Phase, the action taken will depend on the final dose tolerated. If the final tolerated dose is below 300 mg, then all subsequent dosing is to be discontinued, the subject considered an escalation failure, and asked to return to the CRC 14 days following the last dose of AR101 (CPNA) to undergo an Early Termination Visit. If the final tolerated dose is ≥ 300 mg, then the dose should be reduced to the last tolerated dose and continued long-term without further escalation.

Any subject deemed to have severe symptoms including hypoxia, hypotension, or change in mental status (stage 3 defined in **Appendix 3**: Anaphylaxis Staging System) or 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 active therapy.

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

Any subject who discontinues buildup dosing due to repeated allergic reactions to the AR101 (CPNA) will have his/her mechanistic blood draw (refer to **Section 8**) within approximately 1 week of discontinuation of therapy.

6.6.3 Treatment for Reactions during the Buildup Phases: Pharmacological and Supportive Treatments

Treatment of individual reactions should be with an antihistamine and/or epinephrine, along with IV fluids, a beta-agonist (e.g., albuterol, by inhaler or nebulizer), oxygen, and glucocorticosteroids, as indicated. Generally, for mild symptoms requiring treatment, the subject should receive antihistamines. Generally, for moderate symptoms requiring treatment, the subjects should receive antihistamines and/or epinephrine as indicated. If severe anaphylaxis (stage 3 defined in **Appendix 3**: Anaphylaxis Staging System) occurs at any time, dose escalation will stop and the dose will be reduced to the last tolerated dose and the subject continued on that dose as long-term maintenance without further escalation.

Antihistamines

If a subject receives antihistamines only, the dose escalation can be continued. If symptoms during a build-up day require antihistamines in multiple doses (> 2) or in combination with other medications (except epinephrine), there should be a dose reduction by 1-2 doses with the next dose given in the CRC. If epinephrine is administered, then a different course of action is to be taken (see below). If dose escalation fails or requires treatment after two more escalation attempts each spaced 2 to 4 weeks apart, no additional dose escalation is to be attempted. If the final tolerated dose is below 300 mg, then all subsequent dosing is to be discontinued, the subject considered an escalation failure, and asked to return to the CRC 14 days following the last dose of AR101 (CPNA) to undergo an Early Termination Visit. If the final tolerated dose is ≥ 300 mg, then the dose should be reduced to the last tolerated dose and continued long term without further escalation.

Epinephrine - General

Any reaction (in clinic or at home) that requires two or more doses of epinephrine will halt further dose escalation for this individual. If the final tolerated dose is below 300 mg, then all subsequent dosing is to be discontinued, the subject considered an escalation failure, and asked to return to the CRC 14 days following the last dose of AR101 (CPNA) to undergo an Early Termination Visit. If the final tolerated dose is ≥ 300 mg, then the dose should be reduced to the last tolerated dose and continued long term without further escalation.

Epinephrine - Clinic

If a single administration of epinephrine is required during escalation in the clinic, the dose of study medication is to be reduced by two increments, or to the last tolerated dose (at the physician's discretion), and dose escalation is to continue.

If a single administration of epinephrine is required a second consecutive time during this escalation attempt, the dose should be reduced by two doses, and the subject continued on that dose for 6-8 weeks. After 6-8 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 this escalation attempt, no further attempts at dose escalation should be made. If the final tolerated dose is below 300 mg, then all subsequent dosing is to be discontinued, the subject considered an escalation failure, and asked to return to the CRC 14 days following the last dose of AR101 (CPNA) to undergo an Early Termination Visit. If the final tolerated dose is ≥ 300 mg, then the dose should be reduced by two doses and the subject continued on that dose as long-term maintenance without further escalation.

Epinephrine - Home

If a single administration of epinephrine use occurs 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. The subject should return to clinic for an observed dose prior to resuming any dosing at home.

6.6.4 Reactions during Plateau Phase

This phase consists of the subject receiving the 300 mg daily dose of peanut OIT for a targeted duration of approximately 3 months.

In the event that one or two episodes of dose reduction from a stable dose of 300 mg/d are required during the Plateau Phase, the Plateau Phase may be extended up to an additional 12 weeks (to a maximum of 24 weeks) on an individual basis. Temporary dose reductions instituted at the investigator's discretion, while a subject is suffering from symptoms of an upper respiratory infection or influenza, or during menses (c.f., **Section 6.6.2**), will count as one of the two allowable dose reduction episodes, if the reduced dose is maintained for > 3 days (in which case the subject is to maintain the new, reduced, dose for 2 weeks before re-escalating biweekly in a stepwise fashion). Dosing of an individual subject during the Plateau Phase will be discontinued for any of the following reasons:

- Requiring more than two episodes of dose reduction from a stable dose of 300 mg/d (dose adjustments within the first 3 days a dose reductions do not constitute separate episodes of dose reduction)
- Following a dose reduction, failure to re-escalate after 3 attempts
- Inability to maintain a dose of 300 mg/d for at least the last 4 consecutive weeks of the Plateau Phase.

The procedures for escalating back up to a dose of 300 mg/d following a dose reduction in the Plateau Phase will follow the same re-escalation rules as for the Low-dose Buildup Phase.

The subject will continue to follow a peanut-avoidant diet for the duration of the study.

6.6.5 Reactions during the Extended Maintenance Phase

This phase consists of the subject receiving 2000 mg/d or the maximum achieved daily dose of peanut OIT, ≥ 300 mg.

During the Extended Maintenance Phase the frequency of visits will gradually decrease over time from every 2 weeks to every 3 months, as described in **Sections 6.3.12 - 6.3.15**.

All subjects will continue to follow a peanut-avoidant diet for the duration of the study.

For any noted symptoms during the maintenance phase, the **same** study dosing rules for the High-dose Buildup Phase will be followed.

Figure 6-2: Schematic for Initial (Visit 01) Day Escalation

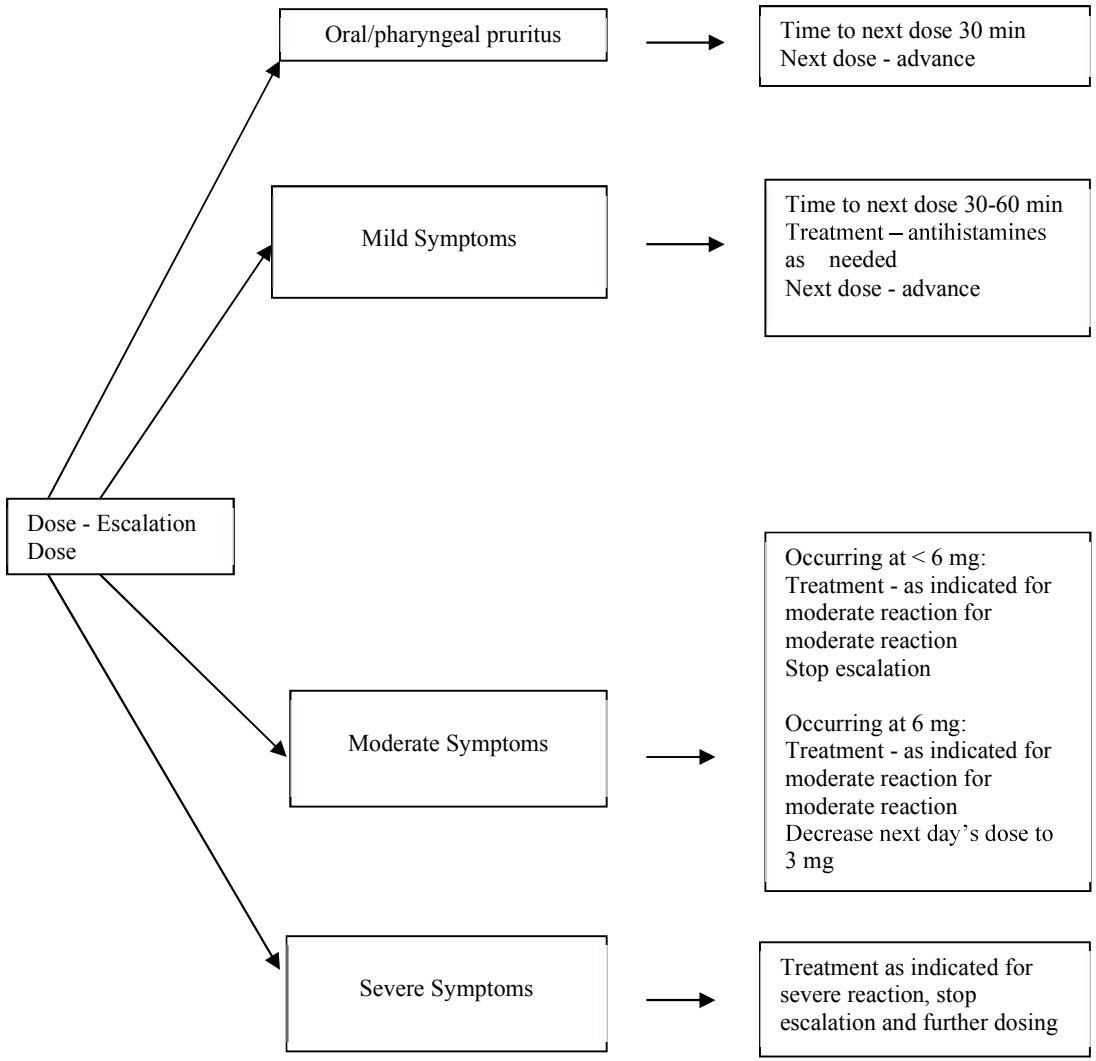
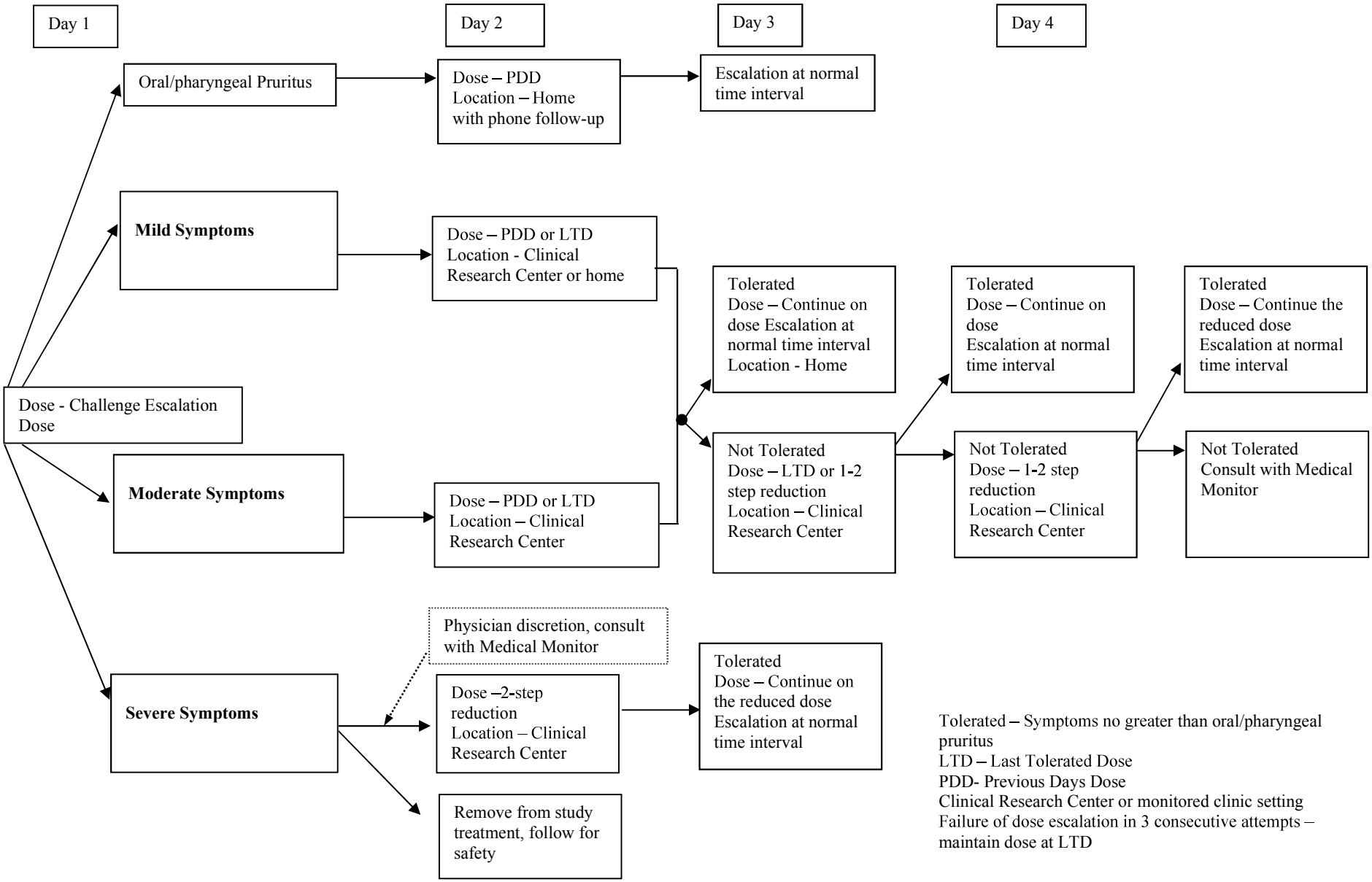


Figure 6-3: Schematic for Buildup Phase Dose Escalation – Day of Symptom



6.7 Missed Peanut OIT Doses at any Phase of the Study:

Missed peanut OIT doses at any phase of the study can pose a significant risk to the enrolled subjects. The algorithm for missed consecutive doses of study product is as follows:

- Miss 1 dose – The next dose would be the current dose and could be given at home
- Miss 2 doses in a row – The next dose would be the current dose and could be given at home
- Miss 3 doses in a row – The next dose would be the current dose and would be given under observation (CRC)
- Miss 4 doses in a row – The next dose would be the current dose and would be given under observation (CRC)
- Miss 5-7 doses in a row – Initiate the next dose as approximately 50% of the last tolerated dose (use the study dose from the Buildup Schedule that is closest to 50%). Dose re-escalation would occur under observation in the CRC with an escalation no sooner than weekly and no longer than every 4 weeks with dose increases of 1-dose level at each escalation. If symptoms occur, the dosing symptom rules in the buildup phase would apply.
- Additionally; excessive missed doses due to noncompliance, i.e., 3 consecutive days missed on 3 occasions within a 9-month period, constitutes an individual stopping rule and the subject should no longer take the study product.
- If study product has been withheld for 8-14 consecutive days as treatment for an AE or due to a study product dispensing error, dosing may be reinitiated at approximately 25% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 25% of the last tolerated dose) if the lapse in dosing occurred during an Up-dosing Period. If the lapse in dosing occurred during the Plateau or Extended Maintenance Period, dosing may, at the investigator's discretion, be reinitiated at 50% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 50% of the last tolerated dose). The reduced dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1-dose level occurring no more frequently than weekly and no less frequently than every 4 weeks until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the Up-dosing period apply.
- Missing > 14 consecutive days of therapy for any reason constitutes an individual stopping rule and the subject should no longer take the study product but would be followed longitudinally.
    - Group 1 subjects in the Low-dose Buildup Phase must also be able to reach 300 mg by Week 34.

Subjects who fulfill a stopping rule will be asked to return to the CRC 14 days following their last dose of AR101 (CPNA) to undergo an Early Termination Visit (see **Section 6.3.17**).

6.8 Double-Blind Placebo-Controlled Food Challenge

The subject will be off antihistamines for an appropriate length of time (5 half-lives of the antihistamine that is being used). Oral food challenges will be undertaken under direct medical supervision in a CRC or food challenge area with emergency medications and staff immediately available and will follow established study procedures. Prior to the DBPCFC, subjects will be assessed for an exacerbation of asthma as determined by active wheezing or a peak expiratory flow rate < 80% of predicted. When no adverse symptoms are detected during physical exams or assessments, oral food challenges may also be delayed based on subject's or subject family's report of illness, at the investigator's discretion. A uniform approach for food challenges will be used. Frequent assessments will be made for symptoms affecting the skin, gastrointestinal tract, cardiovascular system, and/or respiratory tract. Dose-limiting symptoms, typically objective symptoms (signs), indicate a positive reaction and termination of dosing.

6.9 Skin Prick Test

Subjects will have skin prick tests performed using study approved procedures for food allergens. 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.

6.10 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 (i.e., 2 days before or 2 days after the scheduled visit date) for all phases of the study up until Week 24 of the Extended Maintenance Phase.
- Starting at Week 24 of the Extended Maintenance Phase, the permissible window around study visits will be extended to 1 week before or 1 week after a planned in-clinic dosing visit (i.e., ±1 week).
- The Early Termination Visit is to occur 14 days after the last dose of AR101 (CPNA). The permissible window is (minus 3 days to plus 7 days).
- Study visits for scheduled blood draws or DBPCFC should take place within 2 weeks of the scheduled visit.

6.11 Study Blinding Procedures

The study is unblinded with the exception of the oral food challenges. All food challenges are performed in a double-blind manner.

6.11.1 Securing Blinding and Randomization Information

Aimmune Therapeutics or its contractors will manufacture, package, label, store, and distribute drug. During site visits, the site monitor will check pharmacy logs to ensure that ARC002 group assignments are appropriate based on randomization assignments from ARC001.

6.11.2 Requirements for an Unblinding

Not applicable.

6.11.3 Breaking the Blind

Not applicable.

6.11.4 Documenting an Unblinding

Not applicable.

7. Safety Monitoring

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

7.1 Definitions for Recording of Safety Events

All safety events observed under this protocol are recorded in the data system. Some safety events arising under certain defined conditions are recorded on specific eCRFs and/or specific reporting forms as follows.

- Accidental exposures to food allergens are recorded on a Food Allergy Episode Log eCRF. If these events result in an AE, the AE is recorded as described below. These do not include protocol-specified exposures to food challenge reagents or study treatments.
- Any in-clinic dose-related symptoms will be recorded on the Dosage of Study Product/Reaction eCRF. In addition, symptoms should be assessed by the PI to determine if they constitute one or more than one AE, as well as the severity and relatedness to study-product, and recorded on the AE eCRF (please refer to eCRF Completion Guidelines for more detail).
- Dose-related symptoms recorded in the subject diary, should be assessed by the PI to determine if they constitute one or more than one AE, as well as the severity and relatedness to study-product, and should be recorded on the AE eCRF (please refer to eCRF Completion Guidelines for more detail).
- Events occurring after a subject has signed the informed consent form that meet the definition of anaphylaxis (**Appendix 3**) will be recorded in the Anaphylaxis Reaction eCRF. In addition, anaphylaxis events will be recorded on the Anaphylaxis Reporting Form. Events associated with any of the following must be reported within 24 hours of site knowledge to facilitate expedited reporting.
    - An emergency room (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 3**: Anaphylaxis Staging System.

- Oral food challenge reactions that occur in the clinic are captured on study-specific eCRFs and are not reported on the AE eCRF unless the event is considered a serious adverse event (see below).
- AEs occurring during skin prick test should be recorded on the AE eCRF.
- Serious adverse events (whether or not related to dosing) will be recorded on an adverse event (AE) eCRF and a serious adverse event (SAE) form.

7.2 Accidental Food Allergen Exposure

In order to report the occurrence of a safety event associated with accidental food ingestion, subjects will be instructed to contact the site study coordinator or investigator for any AE. The subject may be asked to return to the site. A Food Allergy Episode eCRF will be completed for each of these events in addition to events where consumption of peanut without a reaction occurs. If the accidental food ingestion safety event meets the definition of an SAE, as defined below, the AE/SAE form will be completed as well.

7.3 Definitions

7.3.1 Adverse Event (AE) or Medical Event

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

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

Adverse reaction is any adverse event caused by the drug.

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

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

1. Death
2. Life-threatening AE (Life-threatening means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred.)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

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

7.3.3 Unexpected Adverse Event

An adverse event is "unexpected" when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, the AR101 (CPNA) Investigator's Brochure or the protocol.

7.3.4 Pregnancy

Pregnancy is not to be considered an adverse event, but it is an important medical event that must be reported and followed. Any pregnancy that occurs during the clinical trial, where the fetus could have been exposed to the study drug, must be followed through the outcome of the pregnancy.

7.4 Data Monitoring Committee

Although the safety of peanut OIT overall is well established, a Data Monitoring Committee (DMC) has been established to monitor the study for safety. The DMC Charter has been adopted.

7.5 Toxicity Grading

The study site assigns toxicity grades to indicate the severity of adverse experiences and toxicities. The CoFAR adopted usage of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.0 for application in adverse event reporting and will likewise be used for this protocol. The allergic reactions in this protocol are defined beyond the NCI-CTCAE system, and include further characterization of anaphylaxis. Anaphylaxis is characterized as mild, moderate, or severe in **Appendix 3**: Anaphylaxis Staging System, independent of the toxicity grade associated with the event. Toxicity grading for allergic reactions including anaphylaxis is modified from the NCI-CTCAE system to be more appropriate for this study population, and is displayed in **Appendix 4**: Allergic Reaction Toxicity Grading.

The NCI-CTCAE v 4.0 was specifically reviewed for this protocol and is appropriate for this study population. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatment-related toxicities.

The NCI-CTCAE provides a term and a grade that closely describes the adverse event. Each participating site will receive copies of the grading scales and event descriptions.

Record adverse events not included in the NCI-CTCAE listing and grade them 1 to 5 according to the General Grade Definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 h), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., 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.

7.5.1 Guidelines for Determining Causality of an Adverse Event

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

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

7.6 Adverse Events Collection Procedures

Adverse events will be evaluated from the onset of the event until the time the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.

Adverse events 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 diary logs (provided to record symptoms between visits)

7.6.1 Reporting Procedures

A multi-page adverse event form will be used allowing all adverse events to be submitted through a single reporting mechanism. Serious adverse events will require additional information reported on additional pages within the Internet data entry system. Source

documents, with subject identifiers redacted, can be scanned and attached to the adverse event form as well. The investigator will treat subjects experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

7.6.2 SAE Reporting Procedures

Serious adverse events will be recorded on the adverse event case report form (CRF). All sites are obligated to report SAEs within 24 h of their occurrence and/or the sites knowledge of the event to the Sponsor or designee. The following attributes will be assigned:

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

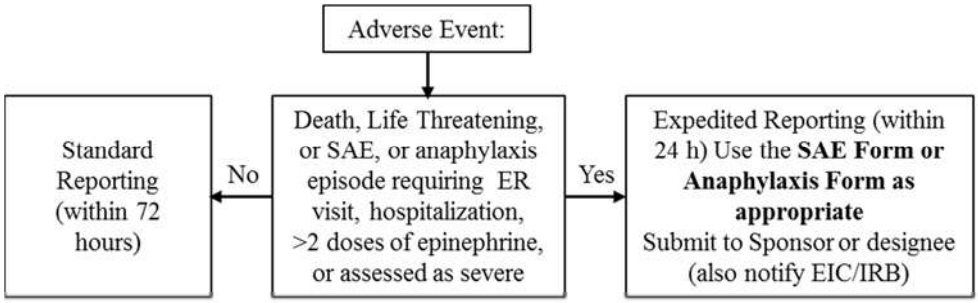
The site investigator will apply his/her clinical judgment to determine whether an adverse event is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator will suspend any trial procedures and institute the necessary medical therapy to protect a subject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

Subsequent review by the Food and Drug Administration (FDA), the DMC, Institutional Review Board (IRB), or the sponsor may suspend further trial treatment or procedures at a site. The study sponsor and the FDA 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 complete an Early Termination Visit and be given appropriate care under medical supervision until the symptoms of any AE resolve or their condition becomes stable.

7.6.2.1 Reporting Criteria

Figure 7-1: Reporting Decisions for Adverse Events



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

7.6.3 Pregnancy Reporting Procedures

In the case of a pregnancy occurring in a clinical trial subject, the Investigator is to have the subject discontinue treatment with the study drug, and obtain the information from the subject on when they became aware of the pregnancy and the anticipated date of delivery. The Investigator must report the pregnancy, within 24 hours of their knowledge of the event, following the same procedure as SAE reporting.

7.7 Serious Adverse Event and Expedited Anaphylaxis Episode Notification

7.7.1 Notifying the Sponsor

Study investigators will provide the Sponsor or designee with data of all SAEs and anaphylaxis events as defined per the protocol on an ongoing basis.

The CRO Medical Monitor is responsible for notifying the sponsor and will do so simultaneously with reporting to the clinical database. As noted above, this should be within 24 h of site awareness of the event. The sponsor's Medical Monitor will review each SAE report and will determine whether the SAE must be reported to FDA on an expedited basis. The final decision for disposition regarding reporting to the FDA rests with the sponsor's Medical Monitor. The IND Sponsor is responsible for submitting the SAE reports to FDA. The IND Sponsor or designee will provide the DMC with copies of any SAE reports submitted to FDA by the Sponsor.

The Sponsor or designee will provide these expedited reports to the individual site investigators. Events that are serious, related to therapy and unexpected will be reported to FDA within 15 days or for deaths and life threatening events within 7 days (per 21 CFR 312.32).

7.7.2 Notifying the Data Monitoring Committee

The Sponsor or designee will provide the DMC with listings of all SAEs on an ongoing basis. Furthermore, the DMC will be informed of expedited reports of SAEs. Reports from DMC ongoing protocol safety reviews will be sent to the investigators.

Per DMC request, centers are instructed to report episodes of anaphylaxis within 24 h of their occurrence and/or the sites being notified of the event to the Sponsor or designee if the event is associated with any of the following:

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

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

7.7.3 Notifying the Institutional Review Board and Ethics Committee

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

7.8 Other Safety Assessments

7.8.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in **Appendix 1**: Schedule of Events. Height and weight will also be recorded. Vital signs will also be assessed, including blood pressure, pulse rate, and body temperature.

7.8.2 Prior and Concomitant Medications

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

7.8.3 Pregnancy Test

All female subjects of child-bearing potential will undergo routine urine pregnancy testing throughout the study at the visits indicated per protocol (refer to **Section 6**).

7.9 Stopping Rules

7.9.1 Overall Stopping Rules

The study will be suspended at any time such that a treatment-associated death occurs, or that the second of two subjects is admitted to the hospital, within 6 months of the first, as a direct consequence of dosing with study medication. Suspension of the study will entail refraining from any dose increases, but will not entail cessation of dosing unless so directed by the FDA, or advised by the DMC and agreed to by the sponsor. Dose escalation will not be resumed until the information has been discussed with FDA and the FDA either concurs with resumption of up-dosing or directs discontinuation of the study.

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

Aimmune Therapeutics additionally reserves the right to discontinue the study at any time for any reason.

7.9.2 Individual Stopping Rules

Individuals may stop the study at any time if they experience subjectively intolerable adverse events or dosing symptoms. They must halt up-dosing and re-start with a reduced dose if more than four days of dosing are missed. Fifteen or more days of missed dosing constitutes an individual stopping rule, as does a significant number of episodes of missed dosing (i.e., three consecutive days on at least three occasions within a 9-month period, due to noncompliance). For additional individual stopping rules, the reader is referred back to **Section 4.3.1**.

Failure to accomplish up-dosing after three attempts will result in halting further up-dosing attempts. Additionally, administration of two or more doses of epinephrine for treatment of a dose-related allergic reaction will result in halting further up-dosing attempts. In either event, if the final tolerated dose is below 300 mg/d, then all subsequent dosing is to be discontinued. The subject will be considered an escalation failure and asked to return to the CRC 14 days following the last dose of AR101 (CPNA) to undergo an Early Termination Visit. If the final tolerated dose is ≥ 300 mg, then the dose should be reduced to the last tolerated dose and continued long term without further escalation.

8. Mechanistic Assays

Complementary studies will be performed to measure humoral immune responses at baseline and at 6 months.

- Measurement of antigen-specific IgE and IgG4 levels
- SPT to peanut

8.1 Peanut-specific Antibody

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

At each of the mechanistic time points, a sample of plasma will be stored for assessment of peanut-specific antibody levels. Total IgE and peanut-specific IgE and IgG4 will be measured using UniCAP. Peanut-specific IgE and IgG4 blood draws will be measured at the end of the Low-dose Buildup Phase (Group 1 only), the end of the Plateau Phase, and the end of the High-dose Buildup Phase. Mechanistic studies will also be performed at 3 months and 6 months into the Extended Maintenance Phase, and at 6-monthly intervals thereafter. The amount of blood to be drawn for IgE and IgG4 assays is determined by individual laboratory protocol.

9. STATISTICAL CONSIDERATIONS

This protocol is primarily an observational assessment of the continued safety and efficacy of OIT over an extended period (≥ 18 months) in subjects who participated in study ARC001.

No formal statistical testing is planned for this protocol. Descriptive statistics will be presented in the following manner:

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

For purposes of summarization, the treatment group assignments in ARC002 are based on the original randomized treatment assignment from ARC001. Namely, Treatment Group 1 is former ARC001 placebo subjects and Treatment Group 2 is former ARC001 active subjects. Data will be summarized in tables for each treatment group, treatment groups combined, treatment phase (as defined in **Section 3.2** Treatment Phases), and across all treatment phases. Data from ARC001 will be combined with ARC002 and will be used to define baseline, as appropriate. Additional details about combining data and handling varying exposure times will be described in the statistical analysis plan. Data will be listed for each subject.

9.1 Study Endpoint Assessment

9.1.1 Primary Endpoint

The primary end-point is the incidence of treatment-related AEs and dosing symptoms occurring with peanut OIT over a protracted treatment period comprising at least 18 months. AEs will be coded to a standard set of terms using the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.0 or later).

9.1.2 Secondary Endpoints

The secondary endpoints are defined in **Section 3.6** and will be summarized descriptively.

9.1.3 Exploratory Endpoint

The exploratory endpoint defined in **Section 3.7** will be summarized descriptively.

9.2 Subject and Demographic Data

9.2.1 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic data, collected from ARC001 and/or ARC002 will be provided for all enrolled subjects. Demographic data will include age, race, sex, body weight and height.

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

9.2.2 Use of Medications

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

9.2.3 Study Completion

The percent of subjects who complete the study, losses to follow-up, times to lost to follow-up and reasons for discontinuation (e.g., adverse events, escalation failures) will be presented.

9.2.4 Adverse Events

Adverse events will be coded on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

9.3 Sample Size and Power Calculations

The primary objective of this study is to assess safety and tolerability of extended exposure to OIT. The sample size for this study is based on the number of eligible subjects from study ARC001 consenting to rollover into the ARC002 open-label extension study. As such, no formal power calculations have been performed.

10. Identification and Access to Source Data

10.1 Web-Based Data Collection and Management System

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

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

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

10.3 Data Management

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

10.4 Access to Data

The investigational sites shall periodically permit authorized representatives of the IND sponsor, and/or regulatory health authorities to examine clinical records and other source documents for the purpose of safety monitoring, quality assurance reviews, audits and evaluation of the study progress throughout the entire study period. The investigator is required by law (21 CFR 312.62) to keep accurate case records for at least 2 years after acceptance of a licensure application and FDA is notified, and record observations to assure the safe conduct of the study.

11. Quality Control and Quality Assurance

11.1 Statement of Compliance

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

11.2 Informed Consent/Assent

The informed consent form is a means of providing information about the study to a prospective subject or subject's parent/guardian and allows for an informed decision about participation in the study. Because the study population will be comprised of a significant percentage of children, parents or legal guardians will be asked to read, sign and date a consent form before a child enters the study, takes study drug, or undergoes any study-specific procedures. Children will sign an assent as appropriate. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The informed consent form will be reviewed to determine whether a revision is required whenever the protocol is amended. A copy of the informed consent will be given to a prospective parent/guardian for review. The attending physician or his/her designee, in the presence of a witness, will review the consent and answer questions, as well as emphasize the need to avoid allergen exposure other than to AR101 (CPNA), and the necessity to continue exposure to AR101 (CPNA) to maintain de-sensitization. The prospective subject or 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.

11.3 Privacy and Confidentiality

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

12. Resource Sharing

All data derived from this study will be sent to the Sponsor or designee for storage and analysis. Subject data will be anonymized to maintain subject confidentiality. All data derived from these studies will be submitted for publication in peer-reviewed scientific journals in a timely manner. The Sponsor will review all manuscripts prior to submission to journals for publication and all abstracts prior to submission to national and international meetings. All data sets will be archived by the Sponsor or designee and may be made available to interested, outside investigators with approval by the Sponsor.

13. Protocol Deviations

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

13.1 Major Protocol Deviation (Protocol Violation)

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

13.2 Non-Major Protocol Deviation

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

13.3 Reporting and Managing Protocol Deviations

Non-Major Protocol Deviations related to data entry or visit adherence are captured within the data system and are not additionally reported on a separate CRF.

The study site Principal Investigator has the responsibility to document and report protocol violations/deviations as described in this section, including those identified during site monitoring visits or other forms of study conduct review, and develop appropriate corrective action plans.

Appendix 1: Schedule of Events

Appendix 1-A: Schedule of Events – Group 1 (ARC001 Placebo Subjects) Screening to Plateau Phase

Appendix 1-B: Schedule of Events – Group 1 (ARC001 Placebo Subjects) – Post Plateau Phases

Appendix 1-C: Schedule of Events – Group 2 (ARC001 Active Subjects) – Screening to Plateau Phase

Appendix 1-D: Schedule of Events – Group 2 (ARC001 Active Subjects) – Post Plateau Phases

Appendix 1-A: Schedule of Events – Group 1 (ARC001 Placebo Subjects) Screening to Plateau Phase

Visit	ARC001 Exit(ARC002 Rollover)	Initial Escalation	Low-dose Buildup Phase			Plateau Phase		
			CRC Dosing	Interim Visit	End of Phase Visit	CRC Dosing	End of Plateau Visit	Early Term
	All screening procedures occur during ARC001 Exit Visit	Days 1-3[a]	~every 2 wks for 20-36 wks[b]	Week 12	≤ Week 36	~every 4 wks for 12-24 wks		
Informed consent/assent	*							
Confirm ARC001 treatment	*							
Inclusion/Exclusion	*							
Medical/allergy history	*			X	X	X	X	X
Diet history	*	X		X	X		X	X
Concomitant medications	*	X	X	X	X	X	X	X
Physical exam[c]	*	X	X	X	X	X	X	X
Vital signs (BP, PR, temp)	*	X	X	X	X	X	X	X
PEFR[d]	*	X	X	X	X	X	X	X
Urine pregnancy test[e]	*			X	X		X	X
Blood draw for peanut-specific IgE, IgG4[f]	*				X		X	X
Optional blood draw for ITN/Benaroya exploratory analysis[g]	*	X[h]			X[i]		X[i]	
Skin prick test	*				X		X	X
Administration of OIT at site		X	X	X		X		
Physician Global Assessment	*				X		X	X
Dispensing/return of unused AR101 (CPNA)		X	X	X	X	X	X	X
Dose assessment[j]			X					
Double-blind placebo-controlled food challenge (DBPCFC)					X[k] (600 mg max)		X[l] (1000 mg max)	
Monitor for allergic symptoms		X	X	X	X	X	X	X
Monitor for compliance			X	X	X	X	X	X
Adverse events[m]		X	X	X	X	X	X	X
Telephone Follow-up[n]		X	X	X	X	X	X	

Appendix 1-A: Schedule of Events – Group 1 (ARC001 Placebo Subjects) Screening to Plateau Phase (continued)

Footnotes:

a) The Initial Escalation Visit will be scheduled for 5-10 days after the ARC001 Exit/ARC002 Rollover Visit. See **Table 3-1** for dose escalation schedule. Subjects will begin home dosing at their maximum tolerated dose (3 or 6 mg).
Day 1: Escalation to at least 3 mg (subjects who cannot tolerate 3 mg are escalation failures).
Day 2: Confirm tolerance of Day 1 dose (3 or 6 mg).
Day 3: Subjects who tolerated 6 mg on Day 1, but had moderate or severe symptoms at 6 mg on Day 2, will return to clinic for dosing at 3 mg. If 3 mg is not tolerated, subject is an escalation failure.

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

c) Physical exam to include height and weight. At the investigator's discretion, symptom-directed physical exams may be completed at up-dosing visits during the Low-dose Buildup Phase, and CRC Dosing visits during the Plateau Phase. Full physical exams are to be conducted at all other visits.

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

e) For females of childbearing potential.

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

g) Optional blood draw for subjects ≥ 30 kg only. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml total; analysis by Immune Tolerance Network (ITN)/Benaroya.

h) One blood draw to be collected 5-10 days after the ARC001 Exit DBPCFC.

i) Two blood draws to be collected: one draw prior to the DBPCFC, and a second draw 5-10 days post-DBPCFC.

j) During the Low-dose Buildup Phase, at each CRC Dosing Visit an assessment will be made to determine whether to maintain the subject at the current dose or to up-dose to the next level.

k) Eligible subjects, those subjects who up-dose to 300 mg and maintain for 2 weeks, will undergo a DBPCFC at the end of Low-dose Buildup Phase Visit.

l) Eligible subjects, those who up-dose to 300 mg and maintain for 4 weeks, will undergo a DBPCFC at the end of Plateau Phase Visit. Subjects who tolerate the DBPCFC at ≥ 300 mg have the option to enter the Optional High-dose Buildup Phase.

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

n) Phone calls will occur 1 week after each escalation visit to assess dosing compliance and allergic symptoms. Schematic for symptoms is described in **Figure 6-3**.

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

Appendix 1-B: Schedule of Events – Group 1 (ARC001 Placebo Subjects) – Post Plateau Phases

	Optional High-dose Buildup Phase[a]				Extended Maintenance				
Visit	**Initiation Visit**	**CRC Dosing**	**Interim Visit**	**End of Phase Visit[b]**		**Interim Visit**	**Periodic Follow-up**	**Study Exit Visit**	**Early Term /Exit**
		~every 2 wks for up to ~30 wks[c]	**12 Weeks Post Initiation**		**Week 2 & Week 6 Visit**	**12 Weeks After Start of Maintenance**	**Weeks 24, 36, 48, etc.**		
Supplemental Informed Consent	X							X	X
Medical/allergy history			X	X	X	X	X	X	X
Diet history			X	X				X	X
Concomitant medications		X	X	X	X	X	X	X	X
Physical exam[d]		X	X	X	X	X	X	X	X
Vital signs (BP, PR, temp)	X	X	X	X	X	X	X	X	X
Peak expiratory flow rate (PEFR)[e]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[f]			X	X		X	X	X	X
Blood draw for peanut specific IgE, IgG4				X		X	X[g]	X	X
Skin prick test				X		X	X[g]	X	X
Administration of OIT at site	X	X	X	X	X	X	X		
Physician Global Assessment				X				X	X
Dispensing/return of unused study drug	X	X	X	X	X	X	X	X	X
Dose assessment[h]		X							
Open-label food challenge (OFC)								X[k]	
Monitor for allergic symptoms	X	X	X	X	X	X	X	X	X
Monitor for compliance	X	X	X	X	X	X	X	X	X
Adverse events[i]	X	X	X	X	X	X	X	X	X

	Optional High-dose Buildup Phase[a]				Extended Maintenance				
Visit	**Initiation Visit**	**CRC Dosing**	**Interim Visit**	**End of Phase Visit[b]**		**Interim Visit**	**Periodic Follow-up**	**Study Exit Visit**	**Early Term /Exit**
		~every 2 wks for up to ~30 wks[c]	**12 Weeks Post Initiation**		**Week 2 & Week 6 Visit**	**12 Weeks After Start of Maintenance**	**Weeks 24, 36, 48, etc.**		
Telephone Follow-up[j]	X	X	X	X	X	X	X		
EQ-5D-5L Questionnaire								X[l]	X[l]
TSQM-9 Questionnaire								X	X
Parent/Patient Exit Survey								X	X
Peanut Allergy Interview								X[l]	X[l]

Appendix 1-B: Schedule of Events – Group 1 (ARC001 Placebo Subjects) Post Plateau Phases (continued)

Footnotes:

a) Subjects who do not consent to the High-dose Buildup Phase will proceed directly to the Extended Maintenance Phase.
b) Subjects must maintain dosing at 2000 mg (or their MTD) for two consecutive weeks before completing the End of Optional High-dose Buildup Phase Visit. This visit will also serve as the Initiation Visit for the Extended Maintenance Phase.
c) Subjects return to clinic every 2 weeks for up-dosing to a target maximum of 2000 mg, following the dose escalation schedule in **Table 3-3,** unless up-dosing is delayed due to allergic reaction.
d) Physical exam to include height and weight. At the investigator's discretion, symptom-directed physical exams may be completed at CRC Dosing Visits during the Optional High-dose Buildup Phase, and Periodic Follow-up Visits during the Extended Maintenance Phase. Full physical exams are to be conducted at all other visits.
e) Peak expiratory flow rate (PEFR): To be conducted prior to any DBPCFC, 3 attempts should be made with the best value recorded. PEFR should be measured at the same time for each visit assessment. If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.
f) For females of childbearing potential.
g) Starting at the Week 24 Extended Maintenance Phase visit, skin prick testing and blood draw for peanut-specific IgE and IgG4 measurement will be conducted at alternate 3-month visits (i.e., Week 24, Week 48, etc.).
h) During the High-dose Buildup Phase, at each CRC Dosing Visit an assessment will be made to determine whether to maintain the subject at the current dose or to up-dose to the next level.
i) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.
j) Phone calls will occur 1 week after each escalation visit to assess dosing compliance and symptoms. Schematic for symptoms is described in **Figure 6-3**.

k) Subjects who complete the Extended Maintenance Phase and consent to an optional OFC will undergo an OFC to a cumulative dose of 4043 mg of peanut protein. Once completed together with all other exit visit procedures the subject will exit the study
l) EQ-5D-5L Questionnaire and optional peanut allergy interview to be completed by telephone following completion of the study.

Note: BP= blood pressure; PR = pulse rate; temp = body temperature; OIT = oral immunotherapy; OFC = Open-label food challenge

Appendix 1-C: Schedule of Events – Group 2 (ARC001 Active Subjects) – Screening to Plateau Phase

	ARC001 Exit[a] (ARC002 Rollover)	**Plateau Phase**			
Visit	**Screening & Plateau Phase Initiation** procedures occur during ARC001 Exit Visit	**Optional ITN/Benaroya Blood Draw**[b] (5-10 days after ARC001 Exit DBPCFC)	**Plateau (~every 4 wks for 12-24 wks)**[c]	**End of Plateau**	**Early Termination**
Informed consent/assent	*				
Confirm ARC001 treatment assignment	*				
Inclusion/exclusion criteria	*				
Medical/allergy history	*		X	X	X
Concomitant medications	*		X	X	X
Physical exam, including weight and height[d]	*		X	X	X
Vital signs (BP, PR, temperature)	*		X	X	X
Peak expiratory flow rate (PEFR)[e]	*		X	X	X
Urine pregnancy test[f]	*			X	X
Diet history	*			X	X
Blood draw for peanut-specific IgE, IgG4	*			X	X
Optional blood draw for ITN/Benaroya exploratory analysis[g]	*[h]	X		X[i]	
Skin prick test	*			X	X
Administration of OIT at site			X		
Physician Global Assessment	*			X	X
Dispensing/return of unused study drug	*		X	X	X
Double-blind placebo-controlled food challenge (DBPCFC)				X	
Monitor for allergic symptoms	*		X	X	X
Monitor for compliance			X	X	X
Adverse events[j]	*		X	X	X
Telephone Follow-up[k]	*		X	X	

Appendix 1-C: Schedule of Events – Group 2 (ARC001 Active Subjects) – Screening to Plateau Phase (continued)

Footnotes:

a) The Plateau Phase Initiation will take place during the ARC001 Exit /ARC002 Rollover Visit.
b) Visit is only for subjects who have consented to the additional optional blood draw for ITN/Benaroya exploratory analysis.
c) Dosing is to be maintained at 300 mg/d unless dose reduction is required.
d) At the investigator's discretion, symptom-directed physical exams may be completed at CRC Dosing visits during the Plateau Phase. Full physical exams are to be conducted at all other visits.
e) PEFR to be conducted prior to any DBPCFC. Three attempts are to be performed with the best value taken; should be measured at the same time for each visit assessment. If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.
f) For females of childbearing potential.
g) Optional blood draw for subjects ≥ 30 kg only. No more than 5 ml/kg may be drawn, up to a maximum of 60 ml total; analysis by Immune Tolerance Network (ITN)/Benaroya.
h) A single pre-DBPCFC blood draw will be collected at the ARC001 Exit/ARC002 Rollover Visit.
i) At the End of Plateau Phase Visit, two blood draws will be completed: one draw prior to the DBPCFC and a second draw 5-10 days following the DBPCFC.
j) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.
k) Phone calls will occur 1 week after each escalation visit to assess dosing compliance and symptoms. Schematic for symptoms is described in **Figure 6-3**.

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

Appendix 1-D: Schedule of Events – Group 2 (ARC001 Active Subjects) – Post Plateau Phases

	Optional High-dose Buildup Phase[a]				Extended Maintenance				
Visit	**Initiation**	**CRC Dosing ~every 2 wks for up to ~30 wks[c]**	**Interim Visit Week 12**	**End of Phase Visit[b] ≤ Week 30**	**Week 2 & Week 6 Visit**	**Interim Visit 12 Weeks After Start of Maintenance**	**Periodic Follow-up Wks 24, 36, 48, etc.**	**Study Exit Visit**	**Early Term/ Exit**
Supplemental Informed Consent	X							X	X
Medical/allergy history			X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X
Physical exam[d]		X	X	X	X	X	X	X	X
Vital signs (BP, PR, temperature)	X	X	X	X	X	X	X	X	X
Peak expiratory flow rate (PEFR)[e]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[f]			X	X		X	X	X	X
Diet history			X	X				X	X
Blood draw for peanut specific IgE, IgG4				X		X	X[g]	X	X
Skin prick test				X		X	X[g]	X	X
Administration of OIT at site	X	X	X	X	X	X	X		
Physician Global Assessment				X				X	X
Dispensing/return of unused study drug	X	X	X	X	X	X	X	X	X
Dose assessment [h]		X							
Open-label food challenge (OFC)								X[k]	
Monitor for allergic symptoms	X	X	X	X	X	X	X	X	X
Monitor for compliance	X	X	X	X	X	X	X	X	X
Adverse events [i]	X	X	X	X	X	X	X	X	X

	Optional High-dose Buildup Phase[a]				Extended Maintenance				
Visit	**Initiation**	**CRC Dosing ~every 2 wks for up to ~30 wks[c]**	**Interim Visit Week 12**	**End of Phase Visit[b] ≤ Week 30**	**Week 2 & Week 6 Visit**	**Interim Visit 12 Weeks After Start of Maintenance**	**Periodic Follow-up Wks 24, 36, 48, etc.**	**Study Exit Visit**	**Early Term/ Exit**
Telephone Follow-up [j]	X	X	X	X	X	X	X		
EQ-5D-5L Questionnaire								X[l]	X[l]
TSQM-9 Questionnaire								X	X
Parent/Patient Exit Survey								X	X
Peanut Allergy Interview								X[l]	X[l]

Appendix 1-D: Schedule of Events – Group 2 (ARC001 Active Subjects) – Post Plateau Phases (continued)

Footnotes:

a) Subjects who do not consent to the High-dose Buildup Phase will proceed directly to the Extended Maintenance Phase.
b) Subjects must maintain dosing at 2000 mg (or their MTD) for two consecutive weeks before completing the End of Optional High-dose Buildup Phase Visit. This visit will also serve as the Initiation Visit for the Extended Maintenance Phase.
c) Subjects return to clinic every 2 weeks for up-dosing to a target maximum of 2000 mg, following the dose escalation schedule in **Table 3-3**, unless up-dosing is delayed due to allergic reaction.
d) Physical exam to include height and weight. At the investigator's discretion, symptom-directed physical exams may be completed at bi-weekly CRC Dosing Visits during the Optional High-dose Buildup Phase, and Periodic Follow-up Visits during the Extended Maintenance Phase. Full physical exams are to be conducted at all other visits.
e) PEFR to be conducted prior to any DBPCFC. Three attempts are to be performed and the best value taken; should be measured at the same time for each visit assessment. If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.
f) For females of childbearing potential
g) Starting at the Week 24 Extended Maintenance Phase Visit, skin prick testing and blood draw for peanut-specific IgE and IgG4 measurement will be conducted at alternate 3-month visits (i.e., Week 24, Week 48, etc.)
h) During the High-dose Buildup Phase, at each CRC Dosing Visit an assessment will be made to determine whether to maintain the subject at the current dose or to up-dose to the next level.
i) Adverse events will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the subject completes treatment, whichever comes first.
j) Telephone calls assessing dosing compliance and symptoms will occur 1 week after each escalation. Schematic for symptoms is described in **Figure 6-3**.
k) Subjects who complete the Extended Maintenance Phase and consent to an optional OFC will undergo an OFC to a cumulative dose of 4043 mg of peanut protein. Once completed together with all other exit visit procedures the subject will exit the study
l) EQ-5D-5L Questionnaire and optional peanut allergy interview to be completed by telephone following completion of the study.

Note: BP= blood pressure; PR = pulse rate; temp = body temperature; OIT = oral immunotherapy; OFC = Open-label food challenge

Appendix 2: Evaluation of Asthma

The evaluation of asthma severity will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) classification published August 28, 2007 as described in the table below.

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

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

Appendix 3: Anaphylaxis Staging System

Criteria for Diagnosis[30]

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

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

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

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

Staging System of Severity of Anaphylaxis[29]	
Stage	**Defined By**
1. *Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)*	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)	Marked dysphagia, hoarseness and/or stridor; shortness of breath , wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Appendix 4: Allergic Reaction Toxicity Grading

Current NCI-CTCAE v. 4.03, used for severity grading of most AEs occurring in this study, will NOT be used as the grading system for allergic reactions, defined as disorders characterized by an adverse local or general response from exposure to an allergen. Instead, the CoFAR specific grading system, **Table A4-3**, will be used. The NCI-CTCAE system, **Table A4-1** (below), is provided for information purposes only.

Table A4-1: Current NCI-CTCAE v. 4.03 Grading System for Allergic Reactions

Grade 1 - Mild	Grade 2 - Moderate	Grade 3 – Severe	Grade 4 – Life-Threatening	Grade 5 – Death
Transient flushing or rash, drug fever < 38 degrees C (< 100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death

Current NCI-CTCAE v. 4.03 grading system for anaphylaxis reactions, defined as a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response, will NOT be used in the current study. Instead, the EAACI grading system (see **Appendix 3**), will be used. The NCI-CTCAE system, **Table A4-2** (below), is provided for information purposes only.

Table A4-2: Current NCI-CTCAE v. 4.03 Grading System for Anaphylaxis Reactions

Grade 1 - Mild	Grade 2 - Moderate	Grade 3 - Severe	Grade 4 – Life-Threatening	Grade 5- Death
-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

The NCI-CTCAE grading system for allergic reactions will be superseded by the CoFAR-specific grading system (as displayed in **Table A4-3** below) for the assessment of allergic reactions. And the NCI-CTCAE grading system for anaphylaxis reactions will be superseded by the EAACI system (see **Appendix 3**).

Table A4-3: 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 h), no or minimal medical intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	Symptoms that produce mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting or other symptoms.	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible Symptoms may include Bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated.	Extreme limitation in activity, significant assistance required; significant medical/therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.	Death

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

For an episode of anaphylaxis to be considered an SAE, Aimmune Therapeutics advises that the event satisfy one of the outcome-based definitions of SAE specified in **Section 7.3.2** of the ARC002 Protocol, with the stipulations (denoted in *italics*) indicated. These stipulations follow from, and are consistent with, the criteria for DMC reporting (refer to **Section 7.7.2**):

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

Appendix 6: Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

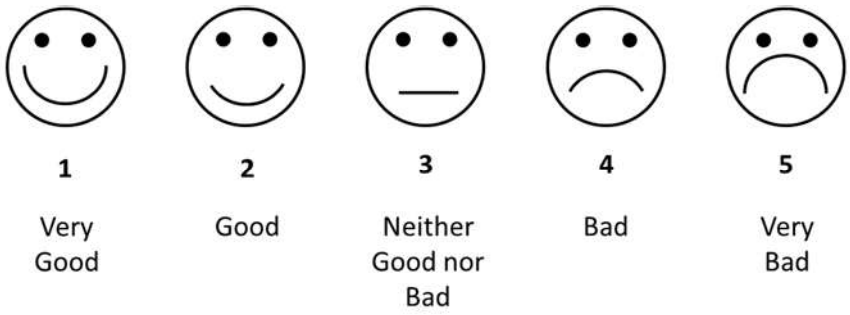
☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Appendix 7: Exit Survey – Parent Completed

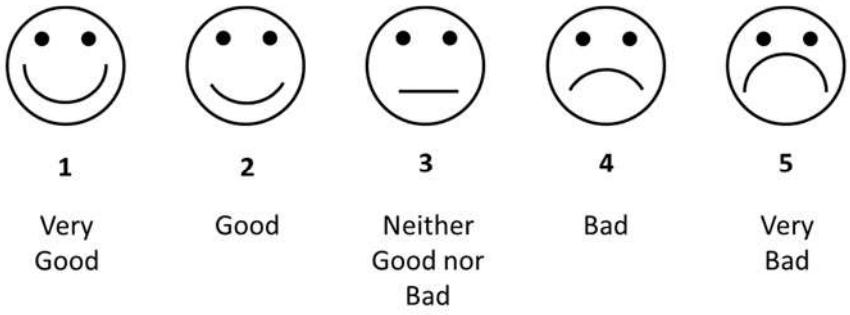
This survey is designed to help us better understand both your own and your child's experiences and satisfaction with the STUDY DRUG. The survey questions will ask you about <u>your child's</u> daily use of the STUDY DRUG for peanut allergy during the study as well as your own and your child's level of satisfaction with the STUDY DRUG.

Please remember that there are no right or wrong answers. Any information you provide is strictly confidential.

1. **Please choose the face that best describes your child's reaction to the taste of the STUDY DRUG?**



2. **Please choose the face that best describes your child's reaction to the aftertaste of the STUDY DRUG?**



3. **How frequently does your child take the STUDY DRUG exactly as instructed?**

   □ Never □ Rarely □ Sometimes □ Almost every time □ Every time

4. **How bothersome was it to go to the clinic for your child to take STUDY DRUG?** Please choose only **one** answer.

   □ Extremely bothersome
   □ Very bothersome
   □ Somewhat bothersome
   □ A little bothersome
   □ Not at all bothersome

5. **How interested would you be for your child to continue taking this STUDY DRUG for as long as it is available to your child?**

   □ Extremely interested
   □ Very interested
   □ Moderately interested
   □ A little interested
   □ Not at all interested

6. **How likely are you to recommend this STUDY DRUG to others?**

   □ Extremely likely
   □ Very likely
   □ Somewhat likely
   □ A little likely
   □ Not at all likely

7. Burden of treatment question

Your child has been treated with STUDY DRUG for his/her peanut allergy. This treatment may have advantages as well as disadvantages. Advantages could be feeling safer, being able to eat out more easily, and feeling less concerned about your child accidentally eating some peanut. Disadvantages could be having troublesome side effects from the STUDY DRUG, having to give your child the STUDY DRUG every day or your child needing to continue to avoid peanut and keep carrying an epinephrine auto-injector.

Overall, how would you weigh the advantages and the disadvantages of the STUDY DRUG?

□ Extremely positive	STUDY DRUG has clear advantages and no important disadvantages
□ Positive	STUDY DRUG has more advantages than disadvantages
□ Slightly positive	STUDY DRUG has somewhat more advantages than disadvantages
□ Neutral	Advantages and disadvantages of the STUDY DRUG are equal
□ Slightly negative	STUDY DRUG has somewhat more disadvantages than advantages
□ Negative	STUDY DRUG has more disadvantages than advantages
□ Extremely negative	STUDY DRUG has clear disadvantages and no important advantages

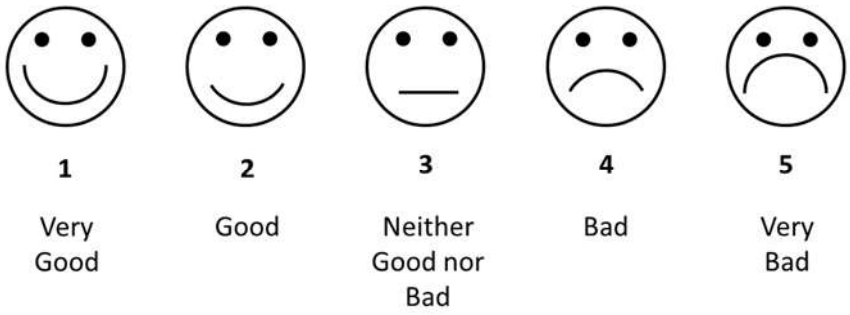
Thank you for taking the time to complete this survey. Your participation and honesty are greatly appreciated.

Appendix 8: Exit Survey – Patient Completed (ages 12 and older)

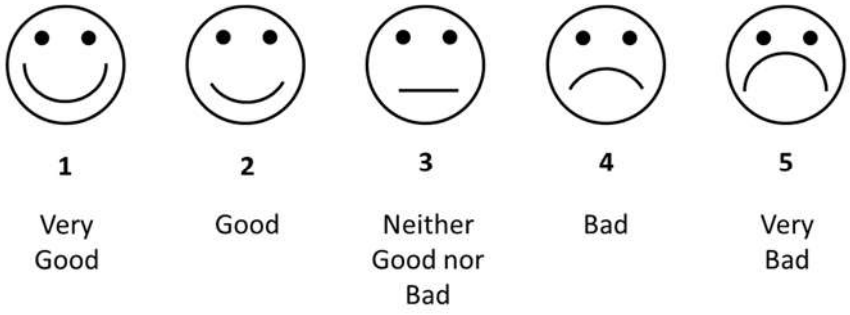
This survey is designed to help us better understand your experiences and satisfaction with the STUDY DRUG. The survey questions will ask you about <u>your</u> daily use of the STUDY DRUG for peanut allergy during the study as well as your level of satisfaction with the STUDY DRUG.

Please remember that there are no right or wrong answers. Any information you provide is strictly confidential.

1. How would you describe the taste of your STUDY DRUG?



2. How would you describe the aftertaste of your STUDY DRUG?



3. **How frequently do you take your STUDY DRUG exactly as instructed?**

   □ Never □ Rarely □ Sometimes □ Almost every time □ Every time

4. **How bothersome was it to go to the clinic to take your STUDY DRUG?** Please choose only **one** answer.

   □ Extremely bothersome
   □ Very bothersome
   □ Somewhat bothersome
   □ A little bothersome
   □ Not at all bothersome

5. **How interested would you be in continuing to take your STUDY DRUG for as long as it is available to you?**

   □ Extremely interested
   □ Very interested
   □ Moderately interested
   □ A little interested
   □ Not at all interested

6. **How likely are you to recommend your STUDY DRUG to others?**

   □ Extremely likely
   □ Very likely
   □ Somewhat likely
   □ A little likely
   □ Not at all likely

7. Burden of treatment question

You have been treated with STUDY DRUG for your peanut allergy. This treatment may have advantages as well as disadvantages. Advantages could be feeling safer, being able to eat out more easily, and feeling less concerned about accidentally eating some peanut. Disadvantages could be having troublesome side effects from the STUDY DRUG, having to take the STUDY DRUG every day or having to continue to avoid peanut and keep carrying an epinephrine auto-injector.

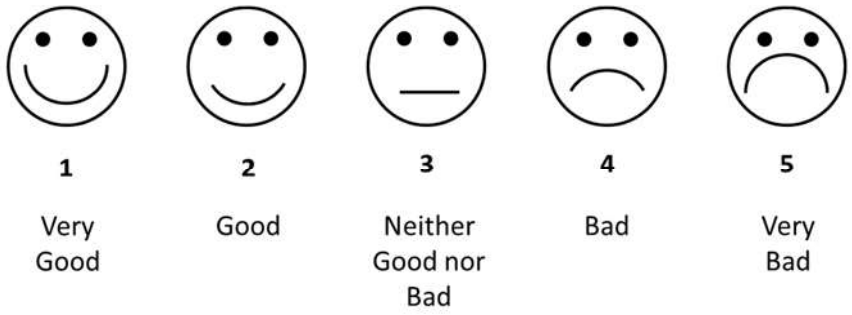
Overall, how would you weigh the advantages and the disadvantages of the STUDY DRUG?

□ Extremely positive	STUDY DRUG has clear advantages and no important disadvantages
□ Positive	STUDY DRUG has more advantages than disadvantages
□ Slightly positive	STUDY DRUG has somewhat more advantages than disadvantages
□ Neutral	Advantages and disadvantages of the STUDY DRUG are equal
□ Slightly negative	STUDY DRUG has somewhat more disadvantages than advantages
□ Negative	STUDY DRUG has more disadvantages than advantages
□ Extremely negative	STUDY DRUG has clear disadvantages and no important advantages

Thank you for taking the time to complete this survey. Your participation and honesty are greatly appreciated.

Children aged 4 – 11 years ONLY:

1. Do you like the taste of your STUDY DRUG?



Appendix 9: Individual One-On-One Interview Guides

INDIVIDUAL ONE-ON-ONE INTERVIEW GUIDE: ADOLESCENTS

ONE-ON-ONE CONCEPT ELICITATION SCRIPT

Good (morning/afternoon/evening) and welcome to our session.

[Introduce self]

Thank you for taking the time to participate in this interview. Today I will talk with you about your peanut allergy, how peanut allergy impacted your life before you started participating in Aimmune's oral immunotherapy trial, and if and how the impact of your peanut allergy may have changed since then. We will also discuss your experience of taking the oral immunotherapy, any positive or negative aspects of the treatment you feel are important. The information you provide will help us better understand how peanut allergy impacts your life, and what improvements or changes are most meaningful and important to allergy sufferers. The session will last approximately one hour.

There are no right or wrong answers. We understand everyone has different experiences. We are interested in what you have to say. Please feel free to share your point of view. Please keep in mind that all information you provide us will be kept confidential. This discussion is being recorded so that we can accurately represent what you are saying during the discussion. The recording will be transcribed and then analyzed. Reports of the results of the discussion will not include your name or any other personal information. The information you share will be very useful to decide how best to measure the impact of peanut allergy on sufferers' lives. If it's okay with you I'd like to begin taping the interview now.

(Begin tape once participant has agreed). Ask

Do you agree that this interview can be taped?

Before we begin there are just a few things we should go over.

- Please speak loudly enough to be clearly heard. Remember that we're tape-recording the session to make sure we do not miss any of your comments.
- My role here is to ask questions and to listen. Some of my questions may seem a bit repetitive and I will try to keep that to a minimum.
- There are just a few other things that I want to let you know. First, I am not a medical doctor, so I am not qualified to give out medical advice. Should you have any questions about your medical condition or your recent/ongoing participation in Aimmune's clinical trial as a result of your participation today, I advise you to speak to your study physician or study site contact about your concerns.
- Any questions before we begin?

I. Background

First, we would like to ask you to give us a general picture of your experience with Peanut Allergy

- How old were you when you were first aware of your peanut allergy?
- Do any of your family members also have peanut allergy?
- Have you ever had an allergic reaction to peanut in your daily life? (Not a food challenge)
    i. How severe was it? (*PROBE: enquire if self managed, required adrenalin shot, hospital visit / stay*)
    ii. How frequently did you used to have allergic reactions to peanut? (Before participating in trial)
    iii. Do you feel confident that you know what to do if you have a reaction?
- Do you feel that your peanut allergy and how it impacts your life is taken seriously?
- How do you think other people who don't have peanut allergy view it?
- Do you have any other food allergies?
    i. Which foods?
    ii. Which of all your food allergies (including peanut) most impacts your quality of life? *(What you do and enjoy in day to day life)*
    iii. Which of all your food allergies (including peanut) most impacts how you feel?

II. Impact of Peanut Allergy - Before Trial

Now I would like to try and understand how living with peanut allergy impacts your day-to-day life.

*[**INTERVIEWER NOTE**: Note salient points throughout ready for comparison to current impacts and changes over time]*

First I would like to ask you **about the time before you started this trial, before you started taking the oral immunotherapy treatment**. I realize this is quite a long time ago – do you think you are able to remember your day-to-day life at that time?

- Can you walk me through a typical day from this time, thinking about all your daily routines and activities whether on a school day or a weekend/holiday?

[PROBE: For example, breakfast or planning lunch, packing your school bag, where you go, what you do, how you behave, school, activities/sports, socializing, friendships, evening routine, how well you sleep anything you need to do, think about, or how you feel because of your peanut allergy]

- What was the most difficult part of having a peanut allergy at that time?
- How would you describe your quality of life at that time?
- How did having peanut allergy make you feel emotionally at that time? ***[INTERVIEWER NOTE****: Note all emotions experienced]*
    - What specifically was the cause of your [emotion]?
    - How did that [emotion] impact your life?

[PROBE: If not spontaneously reported ask about worry/anxiety; self confidence/self esteem; isolation /loneliness; frustration; sadness]

- Were you ever bullied because of your peanut allergy at that time?
    i. How?
- Did school staff ever treat you differently because of your peanut allergy at that time?
    i. How?
- Did you feel that your schoolwork was impacted by your peanut allergy at that time? *[PROBE: missing school, ability to concentrate after allergic reaction*]
- How did having peanut allergy impact your social activities and at that time? [*PROBE: Ever avoided social activities? Why? How often?]*
- How did having peanut allergy impact your relationships/friendships with others at that time? *[PROBE: impact ability to make friends? Impact how well you get along with others?]*
- Did you find some people were insensitive?
    i. If yes: How? And how does this impact you?
- Did having peanut allergy impact your leisure activities or hobbies at that time?
    i. If yes: in what way?

- Are there any ways that living with peanut allergy used to impact your life before you started taking immunotherapy treatment that we haven't discussed?
    i. If yes: in what way?

III. Impact of Peanut Allergy - Now

Now I would like to try and understand how living with peanut allergy impacts your day-to-day life now.

[INTERVIEWER NOTE: First repeat above Section questions but referring to current experiences; Where responses differ to pre-treatment refer to previous response, ask about the change and its importance]

After above complete:

- What are the most important changes you have noticed since taking the immunotherapy treatment? *(If number of changes ask to list in order of importance)*
- What changes have had the biggest impact on your day-to-day life? *(PROBE: If not mentioned probe on emotional impacts (anxiety / worry) and social functioning)*
    i. Why/How?
    - ***[INTERVEWER NOTE: Only ask if reported other food allergies]*** As you have other food allergies, how important is your change in sensitivity to peanut?
- Are there any ways that your life has been impacted since starting this treatment that we haven't discussed that you would like to tell me about?

IV. Treatment Experience

Finally, I would like to talk to you about your experiences related to taking the immunotherapy treatment

- How long have you been receiving the immunotherapy treatment?
- How convenient was it for you to take the treatment?
    i. If not: Why?
- How easy was it for you to take the medicine as instructed?
    - Did you ever miss a dose?
    - How frequently?
    - How did missing treatment affect you?

- What did you think about the taste of the treatment?
- On a scale of 0 to 10, where 0 is not satisfied at all and 10 is as satisfied as you can imagine, how satisfied are you with the treatment you have received?
- How do you think this treatment has improved your quality of life?
- Would you recommend this treatment to others?
- How strictly do you try and avoid peanuts now?
    - Are you worried about "may contain trace of peanut" labeling?
    - Have you ever knowingly or deliberately eaten peanuts in day-to-day life? (Not food challenge)

Lastly, please tell me if there is anything else that you would like to say about your peanut allergy or the immunotherapy treatment that we did not talk about today.

Thank you for your helpful feedback.

Again, we really appreciate the time you have taken to come here and participate in this study.

INDIVIDUAL ONE-ON-ONE INTERVIEW GUIDE: ADULTS

ONE-ON-ONE CONCEPT ELICITATION SCRIPT

Good (morning/afternoon/evening) and welcome to our session.

[Introduce self]

Thank you for taking the time to participate in this interview. Today I will talk with you about your peanut allergy, how peanut allergy impacted your life before you started participating in Aimmune's oral immunotherapy trial, and if and how the impact of your peanut allergy may have changed since then. We will also discuss your experience of taking the oral immunotherapy, any positive or negative aspects of the treatment you feel are important. The information you provide will help us better understand how peanut allergy impacts your life, and what improvements or changes are most meaningful and important to allergy sufferers. The session will last approximately one hour.

There are no right or wrong answers. We understand everyone has different experiences. We are interested in what you have to say. Please feel free to share your point of view. Please keep in mind that all information you provide us will be kept confidential. This discussion is being recorded so that we can accurately represent what you are saying during the discussion. The recording will be transcribed and then analyzed. Reports of the results of the discussion will not include your name or any other personal information. The information you share will be very useful to decide how best to measure the impact of peanut allergy on sufferers' lives. If it's okay with you I'd like to begin taping the interview now.

(Begin tape once participant has agreed). Ask

Do you agree that this interview can be taped?

Before we begin there are just a few things we should go over.

- Please speak loudly enough to be clearly heard. Remember that we're tape-recording the session to make sure we do not miss any of your comments.
- My role here is to ask questions and to listen. Some of my questions may seem a bit repetitive and I will try to keep that to a minimum.
- There are just a few other things that I want to let you know. First, I am not a medical doctor, so I am not qualified to give out medical advice. Should you have any questions about your medical condition or your recent/ongoing participation in Aimmune's clinical trial as a result of your participation today, I advise you to speak to your study physician or study site contact about your concerns.
- Any questions before we begin?

I. Background

First, we would like to ask you to give us a general picture of your experience with Peanut

Allergy

- How old were you when you were first aware of your peanut allergy?
- Do any of your family members also have peanut allergy?
- Have you ever had an allergic reaction to peanut in your daily life? (Not a food challenge)
    i. How severe was it? (*PROBE: enquire if self managed, required adrenalin shot, hospital visit / stay*)
    ii. How frequently did you used to have allergic reactions to peanut? (Before participating in trial)
    iii. Do you feel confident that you know what to do if you have a reaction?
- Do you feel that your peanut allergy and how it impacts your life is taken seriously?
- How do you think other people who don't have peanut allergy view it?
- Do you have any other food allergies?
    i. Which foods?
    ii. Which of all your food allergies (including peanut) most impacts your quality of life?
    iii. Which of all your food allergies (including peanut) most impacts your emotional wellbeing?

II. Impact of Peanut Allergy - Before Trial

Now I would like to try and understand how living with peanut allergy impacts your day-to-day life.

*[**INTERVIEWER NOTE**: Note salient points throughout ready for comparison to current impacts and changes over time]*

First I would like to ask you **about the time before you started this trial, before you started taking the oral immunotherapy treatment**.

- Can you walk me through a typical day from this time, thinking about all your daily routines and activities whether on a college/work day or a weekend/holiday?

    [PROBE: For example, morning routine, where you go, what you do, how you behave, college/work, activities/sports, socializing, friendships, evening routine, how well you

sleep anything you need to do, think about, or how you feel because of your peanut allergy]

- What was the most difficult part of having a peanut allergy at that time?
- How would you describe your quality of life at that time?
- How did having peanut allergy make you feel emotionally at that time? ***[INTERVIEWER NOTE**: Note all emotions experienced]*
    - What specifically was the cause of your [emotion]?
    - How did that [emotion] impact your life?

[PROBE: If not spontaneously reported ask about worry/anxiety; self confidence/self esteem; isolation /loneliness; frustration; sadness]

- [**INTERVIEWER NOTE**: Only ask if age appropriate prior to trial] Were you ever bullied because of your peanut allergy at that time?
    i. How?
- [**INTERVIEWER NOTE**: Only ask if age appropriate prior to trial] Did school staff ever treat you differently because of your peanut allergy at that time?
    i. How?
- Did you feel that your college work / work was impacted by your peanut allergy at that time? *[PROBE: missing college / work, ability to concentrate after allergic reaction*]
- How did having peanut allergy impact your social activities and at that time? [*PROBE: Ever avoided social activities? Why? How often?]*
- How did having peanut allergy impact your relationships/friendships with others at that time? *[PROBE: impact ability to make friends? Impact how well you get along with others?]*
- Did you find some people were insensitive?
    i. If yes: How? And how does this impact you?
- Did having peanut allergy impact your leisure activities or hobbies at that time?
    i. If yes: in what way?

- Did having peanut allergy impact your daily activities (shopping, cooking etc.,) at that time?
    i. If yes: in what way?
- Are there any ways that living with peanut allergy used to impact your life before you started taking immunotherapy treatment that we haven't discussed?
    i. If yes: in what way?

III. Impact of Peanut Allergy - Now

Now I would like to try and understand how living with peanut allergy impacts your day-to-day life now.

[INTERVIEWER NOTE: First repeat above Section questions but referring to current experiences; Where responses differ to pre-treatment refer to previous response, ask about the change and its importance]

After above complete:

- What are the most important changes you have noticed since taking the immunotherapy treatment? *(If number of changes ask to list in order of importance)*
- What changes have had the biggest impact on your day-to-day life? *(PROBE: If not mentioned probe on emotional impacts (anxiety / worry) and social functioning)*
    i. Why/How?
- Are there any ways that your life has been impacted since starting this treatment that we haven't discussed that you would like to tell me about?
- ***[INTERVEWER NOTE: Only ask if reported other food allergies]*** As you have other food allergies, how important is your change in sensitivity to peanut?

IV. Treatment Experience

Finally, I would like to talk to you about your experiences related to taking the immunotherapy treatment

- How long have you been receiving the immunotherapy treatment?
- How convenient was it for you to take the treatment?
    ii. If not: Why?
- What did you think about the taste of the treatment?

- How easy was it for you to take the medicine as directed?
    - Did you ever miss a dose?
    - How frequently?
    - How did missing treatment affect you?
- On a scale of 0 to 10, where 0 is not satisfied at all and 10 is as satisfied as you can imagine, how satisfied are you with the treatment you have received?
- How do you think this treatment has improved your quality of life?
- Would you recommend this treatment to others?
- How strictly do you try and avoid peanuts now?
    - Are you worried about "may contain trace of peanut" labeling?
    - Have you ever knowingly or deliberately eaten peanuts in day-to-day life? (Not food challenge)

Lastly, please tell me if there is anything else that you would like to say about your peanut allergy or the immunotherapy treatment that we did not talk about today.

Thank you for your helpful feedback.

Again, we really appreciate the time you have taken to come here and participate in this study.

INDIVIDUAL ONE-ON-ONE INTERVIEW GUIDE: PARENT/CAREGIVER

ONE-ON-ONE CONCEPT ELICITATION SCRIPT

Good (morning/afternoon/evening) and welcome to our session.

[Introduce self]

Thank you for taking the time to participate in this interview. Today I will talk with you about your child's peanut allergy, how their peanut allergy impacted your life before they started participating in Aimmune's oral immunotherapy trial, and if and how the impact of their peanut allergy may have changed since then. We will also discuss your experience of the required treatment regimen, any positive or negative aspects of the treatment you feel are important. The information you provide will help us better understand how peanut allergy impacts the lives of people with peanut allergy and their families, and what improvements or changes are most meaningful and important to allergy sufferers and their families. The session will last approximately one hour.

There are no right or wrong answers. We understand everyone has different experiences. We are interested in what you have to say. Please feel free to share your point of view. Please keep in mind that all information you provide us will be kept confidential. This discussion is being recorded so that we can accurately represent what you are saying during the discussion. The recording will be transcribed and then analyzed. Reports of the results of the discussion will not include your name or any other personal information. The information you share will be very useful to decide how best to measure the impact of peanut allergy on sufferers' lives and the lives of their parents and families. If it's okay with you I'd like to begin taping the interview now.

(Begin tape once participant has agreed). Ask

Do you agree that this interview can be taped?

Before we begin there are just a few things we should go over.

- Please speak loudly enough to be clearly heard. Remember that we're tape-recording the session to make sure we do not miss any of your comments.
- My role here is to ask questions and to listen. Some of my questions may seem a bit repetitive and I will try to keep that to a minimum.
- There are just a few other things that I want to let you know. First, I am not a medical doctor, so I am not qualified to give out medical advice. Should you have any questions about your child's medical condition or their recent/ongoing participation in Aimmune's clinical trial as a result of your participation today, I advise you to speak to your child's study physician or study site contact about your concerns.
- Any questions before we begin?

I. Background

First, we would like to ask you to give us a general picture of your child's experience with Peanut Allergy

- How old is your child participating in the trial?
    i. How old were they when the trial started?
- How old were they when you were first aware of their peanut allergy?
- How did you feel when you first found out?
    i. What were your main concerns?
- Do you or any of your other family members also have peanut allergy?
- Has your child ever had an allergic reaction to peanut in their daily life? (Not a food challenge)
    i. How severe was it? (*PROBE: enquire if self managed, required adrenalin shot, hospital visit / stay*)
    ii. How frequently did they used to have allergic reactions to peanut? (Before participating in trial)
    iii. Did you feel confident that you knew what to do if they had a reaction?
        a. Did you feel confident that they knew what to do?
- Do you feel that your child's peanut allergy, and how it impacts their life and yours is taken seriously?
- How do you think other people who don't have peanut allergy view it?
- Does your child have any other food allergies?
    i. Which foods?
    ii. Which of all their food allergies (including peanut) most impacts their and your quality of life?
    iii. Which of all their food allergies (including peanut) most impacts their and your emotional wellbeing?

II. Impact of Peanut Allergy - Before Trial

Now I would like to try and understand how living with peanut allergy impacts your day-to-day life.

*[**INTERVIEWER NOTE**: Note salient points throughout ready for comparison to current impacts and changes over time]*

First I would like to ask you **about the time before your child started this trial, before they started taking the oral immunotherapy treatment**.

Can you walk me through a typical day from this time, thinking about all your and your family's daily routines and activities whether it was a school day or a weekend/holiday?

[PROBE: For example, morning routine, where you go, what you do, how you behave, being at work, activities/sports, socializing, friendships, evening routine, how well you sleep anything you need to do, think about, or how you feel because of your child's peanut allergy]

- What was the most difficult aspect of living with your child's peanut allergy at that time?
- How would you describe your quality of life at that time?
- How would you describe your child quality of life at that time?
- How did your child's peanut allergy make you feel emotionally at that time? ***[INTERVIEWER NOTE**: Note all emotions experienced]*
    i. What specifically was the cause of your [emotion]?
    ii. How did that [emotion] impact your life?

    [PROBE: If not spontaneously reported ask about worry/anxiety/sadness and the specific causes: child being in care of others, at school, worry about an allergic reaction, worry about their child's health, worried about their child's social life / socialization, worried about child's emotional wellbeing]

    iii. Did you feel the peanut allergy impacted your child emotionally at that time?
- Was your child ever bullied because of their peanut allergy at that time?
    i. How?

ii. How did that impact you? (How did it make you feel)

- Did school staff ever treat your child differently because of their peanut allergy at that time?
    i. How?
    ii. How did that impact you? *(How did it make you feel)*

- Did you feel that your work was impacted by your child's peanut allergy at that time? *[PROBE: missing work due to allergic reactions, ability to concentrate after allergic reaction*]
    i. How long after your child had a reaction would you feel affected by it?
- How did your child's peanut allergy impact your social activities and at that time? [*PROBE: Ever avoided social activities? Why? How often?]*
- How did your child's peanut allergy make you feel about your child's social activities away from you / home at that time? *(PROBE: restricted activities; worry/anxiety)*
- How did your child's peanut allergy impact your relationships/friendships with others at that time?
    i. How did having peanut allergy impact your child's relationships/friendships with others at that time?
    [PROBE: impact ability to make friends? Impact how well they got along with others?]
- Did you find some people were insensitive?
    i. If yes: How? And how did this impact you?
- Did your child's peanut allergy impact your leisure activities or hobbies at that time?
    i. If yes: in what way?
- Did your child's peanut allergy impact your daily activities (shopping, cooking etc.,) at that time?
    i. If yes: in what way?

- Are there any ways that living with your child's peanut allergy used to impact your life before they started taking immunotherapy treatment that we haven't discussed?

    i. If yes: in what way?

III. Impact of Peanut Allergy - Now

Now I would like to try and understand how living with your child's peanut allergy impacts your day-to-day life now, having started taking the immunotherapy.

[INTERVIEWER NOTE: First repeat above Section questions but referring to current experiences; Where responses differ to pre-treatment refer to previous response, ask about the change and its importance]

After above complete:

- What are the most important changes you have noticed since the immunotherapy treatment? *(If number of changes ask to list in order of importance)*
- What changes have had the biggest impact on your day-to-day life? *(PROBE: If not mentioned probe on emotional impacts (anxiety / worry) and social functioning)*

    i. Why/How?

- Are there any ways that your life, or your child's life, has been impacted since starting this treatment that we haven't discussed that you would like to tell me about?
- ***[INTERVEWER NOTE: Only ask if reported other food allergies]*** As your child has other food allergies, how important is their change in sensitivity to peanut?

IV. Treatment Experience

Finally, I would like to talk to you about your experiences related to the immunotherapy treatment

- How long has your child been receiving the immunotherapy treatment?
- How convenient was the treatment regimen for you?
    - How convenient was it for your child?
- How easy was it for your child to take the medicine as directed?
    - Did they ever miss a dose?
    - How frequently?
    - How did missing treatment affect your child and you?

- What did your child think about the taste of the treatment?
- On a scale of 0 to 10, where 0 is not satisfied at all and 10 is as satisfied as you can imagine, how satisfied are you with the treatment?
- How do you think this treatment has improved your quality of life?
    - How do you think it has improved your child's quality of life?
- Would you recommend this treatment to others?
- How strictly do you and your child try and avoid peanuts now?
    - Are you worried about "may contain trace of peanut" labeling?
    - Have you ever knowingly or deliberately let you child eat peanuts in day-to-day life? (Not food challenge)

Lastly, please tell me if there is anything else that you would like to say about your child's peanut allergy or the immunotherapy treatment that we did not talk about today.

Thank you for your helpful feedback.

Again, we really appreciate the time you have taken to come here and participate in this study.

Appendix 10: References

1. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy, J Allergy Clin Immunol 2007, 119:199-205.
2. Sicherer SH, Wood RA, Stablein D, Burks AW, Liu AH, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy). J Allergy Clin Immunol 2010, 125:1077-1083 e1078. PMCID: PMC2868273
3. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy, J Allergy Clin Immunol 2009, 124:286-291, 291 e281-286. PMCID: PMC2731305.
4. Joshi P. Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food-allergic children. J Allergy Clin Immunol, 2002. 109(6): p. 1019-21.
5. Altschul AS, Scherrer DL, Muñoz-Furlong A, Sicherer SH. Manufacturing and labeling issues for commercial products: relevance to food allergy. J Allergy Clin Immunol, 2001. 108(3): p. 468.
6. Vierk K, Falci K, Wolyniak C, Klontz KC. Recalls of foods containing undeclared allergens reported to the US Food and Drug Administration, fiscal year 1999. J Allergy Clin Immunol, 2002. 109(6): p. 1022-6.
7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics, 1998. 102(1): p. e6
8. Sampson HA, Muñoz-Furlong A, Bock SA, Schmitt C, Bass R, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol, 2005. 115(3): p. 584-91.
9. Frew AJ. 25. Immunotherapy of allergic disease. J Allergy Clin Immunol, 2003. 111(2 Suppl): p. S712-9.
10. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy, 2005. 60(1): p. 4-12.
11. Lehrer SB, Wild LG, Bost KL, Sorensen RU. Immunotherapy for food allergies. Past, present, future. Clin Rev Allergy Immunol, 1999. 17(3): p. 361-81.
12. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol, 1992. 90(2): p. 256-62.
13. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol, 1997. 99(6 Pt 1): p. 744-51.
14. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol, 2011. 127(3): p. 640-6 e1.
15. Varshney P, Jones SM, Scurlock AM, Perry TT, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol, 2011. 127(3): p. 654-60.
16. Bousquet J. Primary and secondary prevention of allergy and asthma by allergen therapeutic vaccines. Clin Allergy Immunol, 2004. 18: p. 105-14.
17. Kapsenberg ML, Hilkens CM, Wierenga EA, Kalinski P. The paradigm of type 1 and type 2 antigen-presenting cells. Implications for atopic allergy. Clin Exp Allergy, 1999. 29 Suppl 2: p. 33-6

18. Secrist H DeKruyff RH, Umetsu DT. Interleukin 4 production by CD4+ T cells from allergic individuals is modulated by antigen concentration and antigen-presenting cell type. J Exp Med, 1995. 181(3): p. 1081-9.

19. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol, 2010. 126(1): p. 83-91 e1.

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

21. Narisety, SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol, 2009. 124(3): p. 610-2.

22. Skripak, JM, Nash SD, Rowley H, Brereton NH, Oh S,et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol, 2008. 122(6): p. 1154-60.

23. McKenna C, Klontz KC. Systemic allergic reaction following ingestion of undeclared peanut flour in a peanut-sensitive woman. Ann Allergy, Asthma & Immunol 1997; 79:234-6.

24. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, et al. for the Consortium of Food Allergy Research. Oral Immunotherapy for Treatment of Egg Allergy in Children. N Engl J Med, 2012 July 19; 367:233-243.

25. Anagnostou K, Islam S, King Y, Foley L, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014 Apr 12;383(9925):1297-304. Epub 2014 Jan 30.

26. Clark AT, Islam S, King Y, Deighton J, et al. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009 Aug;64(8):1218-20. Epub 2009 Feb 17.

27. Wasserman RL, Factor JM, Baker JW, Mansfield LE, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014 Jan-Feb;2(1):91-6.

28. Sampson HA, van Wijk RG, Bindslev-Jensen C, Sicherer S, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology – European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012; 130(8):1260-74.

29. Muraro A, Roberts G, Clark A, Eigenmann PA, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. Allergy. 2007 Aug;62(8):857-71.

30. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

31. The EuroQol Group. EQ-5D-5L User Guide. Version 2.1. April 2015. Accessed at https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf