CLINICAL STUDY PROTOCOL

ARC004
Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-On Study

Protocol Amendment 5.0 – 12 Apr 2018
Reference Numbers: NCT02993107, EudraCT 2016-004941-94

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CLINICAL STUDY PROTOCOL

Protocol Title:	Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-on Study	
Investigational Drug:	AR101, Characterized Peanut Allergen	
Protocol Number:	ARC004	
IND Number:	15463	
EudraCT Number:	2016-004941-94	
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Boulevard Suite 300 Brisbane, CA 94005	
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CLINICAL STUDY PROTOCOL ARC004

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Principal Investigator Protocol Acknowledgement

Protocol ARC004	Version: Amendment 5.0 (Global)
Sponsor: Aimmune Therapeutics, Inc.	Date: 12 Apr 2018
Short Title: PALISADE Follow-on Study	

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

_____

Principal Investigator (Print)

_____ _____

Principal Investigator (Signature) Date

Protocol ARC004 Synopsis	
Title	**Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-On Study**
Short Title	PALISADE FOLLOW-ON STUDY
Clinical Phase	3
IND	15463
IND Sponsor	Aimmune Therapeutics, Inc.
Number of Subjects	Up to approximately 500 peanut-allergic subjects who complete ARC003 and consent to participate in ARC004 will be enrolled.
Objectives	The primary objective of this study is to determine the safety, tolerability and efficacy of AR101 characterized oral desensitization immunotherapy (CODIT™) using alternative maintenance dosing intervals. The secondary objectives are: • To confirm the safety profile of AR101 as measured by the incidence of adverse events (AEs), including serious adverse events (SAEs) • To confirm the efficacy of AR101 through reduction in clinical reactivity, measured in a double-blind, placebo-controlled food challenge (DBPCFC) to a cumulative dose of 4043 mg • To evaluate subjects' quality of life (QoL) and treatment satisfaction during AR101 treatment on daily and nondaily treatment regimens • To evaluate the long-term immunologic effects of AR101 treatment
Study Design	This is an international, multicenter, open-label, 2-arm follow-on study that will explore alternate dosing interval regimens during extended maintenance with AR101. **Group 1 (Placebo Crossovers):** Subjects who complete the placebo arm of ARC003 are eligible to enroll in ARC004. Subjects will enter Group 1 and will undergo initial escalation, up-dosing, and maintenance with AR101 as in the active arm of ARC003. The Initial Escalation Period consists of a step-wise dose-escalation from 0.5 to 3 or 6 mg (as tolerated) on Day 1 and confirmation of the ability to tolerate a single dose of 3 mg on Day 2. The Up-dosing Period is 22 to 40 weeks in duration and consists of dose escalations every 2 weeks up to a maximum of 300 mg/d (as tolerated). The Maintenance Period consists of daily dosing at 300 mg/d for approximately 24 weeks, at which point Group 1 subjects will undergo a DBPCFC to a maximum cumulative dose of 4043 mg peanut protein to test the efficacy of AR101 in ARC003 placebo crossovers after 6 months of daily maintenance. All Group 1 subjects tolerating ≥ 443 mg of cumulative peanut protein will be eligible to continue in ARC004, and enter the Extended Maintenance (EM) Period, initially consisting of ongoing daily maintenance therapy at 300 mg/d. Dependent upon the EM results from ARC004 Group 2 (below), subjects in Group 1 EM will test the gradual lengthening of their dosing interval from daily (QD) to every other day (QOD), twice weekly (BIW), once weekly (QW), and finally every other week (QOW), as tolerated. Lengthening to each level will occur sequentially (QD then QOD then BIW then QW and finally QOW), and only if sufficient evidence exists, based on the analyses of the Group 2 EM subjects and the ongoing safety of Group 1 subjects, to support progression to each level. **Group 2 (Active Rollovers):** Subjects who complete the active arm of ARC003 and tolerate a challenge dose of ≥ 443 mg cumulative of peanut protein at the ARC003 exit food challenge are eligible to enroll in ARC004. Group 2 subjects will have undergone the Initial

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	Escalation, Up-dosing, and Initial Maintenance Periods in ARC003 and will therefore enter the ARC004 EM period directly, where they will be evaluated in 1 of 3 cohorts as outlined below. **Extended Maintenance:** The EM periods will differ between and within the 2 groups in duration and dosing regimen (see below and Figure 1). All EM subjects who complete their dosing regimen, regardless of group or cohort assignment, will have an Exit DBPCFC up to a single highest dose of 2000 mg of peanut protein (4043 mg cumulative). ARC004 will conclude after the last visit for the last subject is completed. **Group 1 Extended Maintenance:** Group 1 subjects who tolerate ≥ 443 mg cumulative peanut protein in the Post-Maintenance DBPCFC will enter the EM period. Subjects who do not tolerate ≥ 443 mg cumulative peanut protein are not eligible to continue for safety reasons. The EM period for Group 1 subjects will initially consist of QD dosing. Conditional upon the safety and DBPCFC outcomes assessed in the Group 2 participants, Group 1 subjects may have their dosing interval serially lengthened from QD to QOD, QOD to BIW, BIW to QW, and QW to QOW, as tolerated. The duration of each of these interval extension periods will be adjusted, based on Group 2's experience, from between 8 to 24 weeks, as tolerated. Following the completion of their longest tested dosing interval, Group 1 subjects will undergo an Exit DBPCFC. **Group 2 Extended Maintenance:** Upon entry into the EM phase of the study (Figure 1), Group 2 subjects will be consecutively enrolled into cohorts that will conditionally explore alternate dosing interval regimens over 28-week study periods, as follows: 1. EM Cohort 1: The first 120 Group 2 subjects to enter ARC004 will make up Cohort 1, and will continue 300 mg of AR101 daily for 28 weeks before undergoing an Exit DBPCFC. 2. EM Cohort 2: The next 50 Group 2 subjects (subjects 121 to 170) enrolling in ARC004 will make up Cohort 2 and will take 300 mg of AR101 QOD for 4 weeks and then BIW (eg, Monday/Thursday) for 24 weeks as tolerated before undergoing an Exit DBPCFC. 3. EM Cohort 3: All remaining Group 2 subjects recruited into ARC004 (subjects 171 to the end) will make up Cohort 3. This cohort will be randomized 1:1:1 to 1 of 3 initial strategies: a) 300 mg QD for 56 weeks followed by an Exit DBPCFC (Cohort 3A) b) 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks followed by an Exit DBPCFC (Cohort 3B) c) 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks, then 300 mg QW for 28 weeks followed by an Exit DBPCFC (Cohort 3C) Group 2 cohorts will produce evidence during the trial concerning the feasibility and safety of adjusting EM dosing from daily to a less frequent schedule. The information that becomes available as each cohort proceeds through the study will be evaluated before determining whether the next cohort is to advance to a longer interval between doses. Lengthening the dosing intervals in subsequent cohorts depends on the safety experience of previous cohorts, which will be reviewed by a Safety Monitoring

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Title	**Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-On Study**
	Committee. Individual and cohort stopping rules are discussed further in Section 7.8.3. **End of Participation in ARC004 and Entry into ARC008:** After the end of participation in ARC004, subjects may enroll in the long-term, open-label extension study ARC008 to continue treatment with AR101 at their current dosing regimen (QD, BIW, QW, or QOW) or switch to AR101 daily dosing, until AR101 becomes commercially available or ARC008 is terminated, as follows: • Subjects on any dosing regimen able to tolerate at least the 600 mg single dose of peanut protein (≥ 1043 mg cumulative) at their ARC004 Exit DBPCFC will continue their current dosing regimen in Treatment Pathway 1 of ARC008 when that study is available. If ARC008 is not available at the study site, these subjects may continue their current dosing regimen and have visits in ARC004 until they can enroll in ARC008. • Subjects who tolerate their nondaily dosing regimen and tolerate at least the 300 mg single dose of peanut protein (≥ 443 mg cumulative) but are unable to tolerate the 600 mg single dose of peanut protein (1043 mg cumulative) at the ARC004 Exit DBPCFC will switch to daily dosing with 300 mg AR101 in Treatment Pathway 1 of ARC008, per investigator discretion. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008. • Subjects on a nondaily dosing regimen who tolerate less than the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC may be eligible for treatment in ARC008 per investigator judgment and after discussion with the medical monitor. If continued treatment with AR101 is determined to be safe, these subjects will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not yet available or able to accept these subjects at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008. • Subjects who do not tolerate their nondaily dosing regimen (described in study procedures for Extended Maintenance) will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008. • Subjects on a nondaily dosing regimen who miss or withhold their dose for > 3 days, including subjects receiving QOD, BIW, or QW dosing who miss or withhold their dose for > 14 days, will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.

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Title	**Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-On Study**
	Subjects are **not** eligible to enroll in ARC008 when continued treatment with AR101 is determined to be unsafe as follows: • Subjects on a daily dosing regimen who are unable to tolerate at least the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC. • Subjects not tolerating their nondaily dosing regimen who begin Repeat Up-dosing in ARC004, but are unable to dose escalate to AR101 300 mg daily and tolerate that dose level for 2 weeks within 26 weeks.
Inclusion Criteria	1. Completion of ARC003 2. Written informed consent and/or assent from subjects/guardians as appropriate 3. Use of effective birth control by female subjects of child-bearing potential
Exclusion Criteria	1. Early discontinuation from ARC003 2. Meets any longitudinally applicable ARC003 exclusion criteria (Appendix 7) 3. (Group 2 only) Failure to tolerate ≥ 443 mg cumulative of peanut protein with no or mild symptoms in the ARC003 Exit DBPCFC 4. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety
Investigational Product and Dispensing	The investigational product is AR101. Doses are expressed as mg of peanut protein. For the Initial Escalation and Up-dosing periods, AR101 will be provided in pull-apart capsules at doses of 0.5, 1.0, 10, 20, and 100 mg. For the Maintenance and EM periods, AR101 will be provided in foil-lined sachets at a dose of 300 mg. AR101 will be shipped directly to investigational sites and will be dispensed according to subject identification number, using an interactive response system. Trained investigational site personnel will administer AR101 directly or dispense AR101 to the subject/ guardian in a manner consistent with the assigned dose level. AR101 is administered by QD dosing during Initial Escalation, Up-dosing, and Maintenance, and by either QD, QOD, BIW, QW, or QOW dosing during EM.
Study Procedures	Procedures will be performed as described in the Schedule of Events (Appendix 1). **Screening:** Potentially eligible subjects will undergo screening for ARC004 concurrently with ARC003 Exit procedures. Subjects who received placebo in ARC003 will be screened for Group 1 and subjects who received AR101 in ARC003 will be screened for Group 2. **Initial Escalation (Group 1 only):** All Initial Escalation doses will be administered by investigational site personnel under direct observation. Eligible subjects will initiate treatment with AR101 on Day 1, starting at a dose of 0.5 mg increasing the dose at 20 to 30 minute intervals to a maximum dose of 6 mg, according to the schedule. Subjects who fail to tolerate the 3-mg dose on Day 1 will be considered escalation failures and will be discontinued. Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on Day 2. Subjects who do not tolerate this confirmatory dose will be discontinued. Subjects who tolerate this confirmatory dose will enter the Up-dosing Period. **Up-dosing Period (Group 1 Only)/Repeat Up-dosing (Subjects Switching to Daily Dosing):** Group 1 subjects will receive AR101 starting at a dose of 3 mg once daily and escalate, per the Up-dosing Schedule, to 300 mg/d. Subjects who have the option to

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	switch to AR101 daily in AR008 may begin daily dosing and have visits in the Repeat Up-dosing Period in ARC004 if ARC008 is not yet available at the study site (described in Study Design). These subjects will start at a dose of 80, 120, or 160 mg (starting dose at investigator's discretion) and gradually escalate every 2 weeks to a maximum of 300 mg once daily, according to the Repeat Up-dosing Schedule. All escalation doses will be administered under direct observation; subsequent doses will be dispensed to the subject/guardian and administered at home. Doses may be adjusted for tolerability or intercurrent illness; the Up-dosing period may thereby be extended from approximately 22 to a maximum of 40 weeks, and the Repeat Up-dosing may be up to a maximum of 26 weeks. Subjects unable to escalate to 300 mg daily within the specified time will be considered escalation failures for analysis purposes and exit the study. Group 1 subjects and subjects switching to daily dosing able to escalate to 300 mg daily and maintain this dose for 2 weeks will have an end of Up-dosing visit/Maintenance visit 1 to enter the Maintenance Period. **Maintenance Period (Group 1 and Subjects Switching to Daily Dosing):** Subjects will continue AR101 300 mg once daily, undergoing directly observed dosing at Weeks 12 and 24 after entering the Maintenance Period. After approximately 24 weeks of daily AR101 treatment at 300 mg as part of the Maintenance Period, Group 1 subjects will undergo a Post-Maintenance DBPCFC with a maximum dose of 2000 mg of peanut protein (4043 mg cumulative), according to the DBPCFC Schedule. Subjects who do not tolerate ≥ 300 mg of peanut protein (443 mg cumulative) will be considered treatment failures and will be discontinued. Group 1 subjects who tolerate ≥ 300 mg of peanut protein (443 mg cumulative) will enter the EM period and continue taking 300 mg of AR101 daily until the results of the alternate regimens explored in Group 2 subjects are known. **Extended Maintenance Period (All Subjects):** Group 1 subjects who tolerate ≥ 443 mg cumulative peanut protein in the Post-Maintenance DBPCFC will enter EM. Subjects who do not tolerate ≥ 443 mg are not eligible to continue for safety reasons. The EM period for Group 1 subjects will initially consist of QD dosing while the first 3 Group 2 cohorts are undergoing evaluation as outlined below. Conditional upon the safety and DBPCFC outcomes assessed in the Group 2 participants, Group 1 subjects may have their dosing interval serially lengthened from QD to QOD, QOD to BIW, BIW to QW, and QW to QOW, as tolerated. The duration of each of these interval extension periods will be adjusted, based on Group 2's experience, from between 8 to 24 weeks, as tolerated. Following the completion of the longest tested dosing interval, Group 1 subjects will undergo an Exit DBPCFC and ARC004 will conclude. Group 2 will consist of 3 cohorts that will each explore a different dose strategy. Eligible Group 2 subjects will be consecutively enrolled into 1 of 3 cohorts as they exit ARC003 and enter the ARC004 EM period directly. Cohort 1 will consist of the first 120 subjects to enter ARC004, and will continue to receive AR101 300 mg on a QD schedule. The next 50 Group 2 subjects to enter ARC004 will form Cohort 2 and be assigned to receive AR101 300 mg QOD for 4 weeks and then BIW (eg, Monday/Thursday) for 24 weeks, as tolerated. Cohorts 1 and 2 will undergo an EM Week 28 Exit DBPCFC to a maximum of 2000 mg (4043 mg cumulative) of peanut protein.

	All remaining Group 2 subjects will enter Cohort 3 in ARC004 EM and will be randomized in a 1:1:1 ratio to ongoing treatment with AR101. • Cohort 3A: QD for 56 weeks • Cohort 3B: QD for 28 weeks followed by QOD for 4 weeks and then BIW for 24 weeks, as tolerated • Cohort 3C: QD for 28 weeks followed by QOD for 4 weeks and BIW for 24 weeks, and finally QW for 28 weeks, as tolerated. At the end of each treatment period, qualifying subjects will undergo a maximum 4043 mg cumulative Exit DBPCFC and complete participation in ARC004. The Exit Visit will complete subject participation in ARC004 with one exception: If a study site has not yet received approval for ARC008, subjects will receive additional AR101 and will continue dosing and visits in ARC004 until ARC008 is able to accept these subjects at the study site. Subjects will return to the study site for an unscheduled visit every 14 weeks to receive AR101 sachets for dosing at home and to ensure subject safety. Throughout ARC004 EM, the first 2 doses at extended dosing intervals (BIW, QW, and QOW) will be administered under direct supervision in the clinic; QOD doses may be initiated at home. Thereafter, the doses will be administered at home as tolerated, and recorded in the subject diary. Investigators may, at their discretion, bring subjects back to the research unit for an observed dose at any time. All AR101 doses will be judged by the investigator to be tolerated or not tolerated according to criteria previously established in ARC003 and specified in Section 6.5.2. Any subject receiving nondaily dosing (QOD, BIW, QW, or QOW) who has 1 related SAE; 1 related AE graded severe; 2 related AEs occurring on separate occasions, both graded moderate; or 3 consecutive doses judged "not tolerated" will be considered a treatment failure in the statistical analysis of each cohort and discontinued from ARC004 for safety reasons. Such subjects may be eligible to enroll in ARC008 on a QD regimen. If a site has not yet received approval for enrollment of subjects into ARC008, the subject will begin daily dosing and have visits in the Repeat Up-dosing period in ARC004. Once the subject reaches the target dose of 300 mg daily and maintains this dose for 2 weeks, that subject will be able to continue this dosing regimen and enroll in ARC008 when available. Early discontinuations due to related AEs, and subjects unable to tolerate a prespecified amount (either ≥ 443 mg or ≥ 1043 mg of cumulative) peanut protein during the Exit DBPCFC, will be considered failures. If failures affect greater than 50% of any cohort, then prolongation of the dosing interval in any subsequent cohort will cease, and the remaining subjects will be administered AR101 300 mg at the longest dosing interval tolerated by a previous cohort (Section 7.8.3). **Early Discontinuations:** Subjects who are discontinued for an AE will have that AE evaluated from the onset until the event is resolved or medically stable, or for 30 days after the Early Discontinuation Visit, whichever comes first. Subjects who are discontinued for reasons other than an AE and who do not enter ARC008 will be followed for safety for 30 days after the last dose of AR101, 2 weeks after the last food challenge, or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is longer. In addition, subjects who are discontinued from further. AR101 dosing due to chronic or recurrent gastrointestinal (GI) AEs will be followed monthly for a minimum of 6 months, or until resolution or stabilization of all GI AEs. For subjects who do not tolerate their nondaily dosing regimen and subjects who switch to daily dosing after missing their nondaily dose for > 3 days, the exit

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	DBPCFC will be omitted before discontinuation from ARC004 and enrollment in ARC008. Subjects who are discontinued will not be replaced.
Study Endpoints	The primary endpoint is the frequency of treatment-related AEs, including SAEs, during the overall study period (from enrollment to the end of EM period). Secondary endpoints include: • Frequency of anaphylaxis • Frequency of use of epinephrine as a rescue medication • Frequency of AEs leading to withdrawal of AR101 • Frequency of AEs in each treatment regimen leading to discontinuation of extended interval dosing • Frequency of GI AEs of interest (GI AEIs) • Frequency of accidental food allergen exposure • In subjects with asthma, change in asthma control using the Asthma Control Test questionnaire see Appendix 2 • Frequency of all above safety endpoints by treatment period • The proportion of subjects in each regimen tolerating ≥ 1043 mg cumulative of peanut protein during their EM Exit DBPCFC • The proportion of subjects in each regimen who tolerate ≥ 443 mg cumulative of peanut protein during their EM Exit DBPCFC • The proportion of subjects in each regimen who tolerate 4043 mg cumulative of peanut protein during their EM Exit DBPCFC • Maximum tolerated dose and change from baseline* at Post-Maintenance** and each EM Exit DBPCFC • Maximum severity of symptoms at each challenge dose at Post-Maintenance** and each EM Exit DBPCFC • Frequency of use of epinephrine as a rescue medication at the Post-Maintenance** and each EM Exit DBPCFC • Change in QoL as assessed by the food allergy related quality of life questionnaire (FAQLQ) and the food allergy independent measure (FAIM) questionnaire • Satisfaction with AR101 treatment as assessed by the Treatment Satisfaction Questionnaire for Medication Version 9 (TSMQ-9) questionnaire and additional questions • Changes in peanut-specific serum IgE and IgG4 levels • Changes in peanut skin prick test (SPT) wheal diameter *Baseline is defined as the Screening DBPCFC from ARC003 for both treatment groups. **Post-Maintenance is defined as the ARC003 Exit DBPCFCs for Group 2.
Study Procedures	The following procedures will be performed according to the scheduled visits tabulated in Appendix 1: • Informed consent (and assent, as age appropriate) • Inclusion/exclusion criteria • Medical/allergy history • Concomitant medications

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	• Physical examination, including height and weight • Vital signs (blood pressure [BP], pulse rate [PR], temperature) • Peak expiratory flow rate (PEFR) in subjects 6 years and older • Spirometry (FEV_1) in subjects 6 years and older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination) • Pregnancy test • Diet (food allergen) history • Blood draw for peanut-specific IgE and IgG4 (including determination of peanut component proteins) (immunoglobulin assays) • Complete blood cell count (CBC), obtained with the same venipuncture as the blood draw for the immunoglobulin assays • Additional blood samples for optional exploratory immunologic studies. These can be obtained at selected centers with the same venipuncture as the blood draw for the immunoglobulin assays (separate informed consent required). • Optional collection of saliva samples for exploratory biomarker development at selected centers (separate informed consent required) • Skin prick test (SPT) • Double-blinded, placebo-controlled food challenges carried out in accordance with PRACTALL guidelines per the schedule • Clinical research center investigational product administration • Dispensing of investigational products for home dosing/return of unused investigational products • Monitoring for dosing compliance • Adverse event (AE) monitoring • Assessment of asthma control using the Asthma Control Test questionnaire and frequency of asthma rescue medication use in subjects with asthma • Change in QoL as assessed by FAQLQ and FAIM questionnaires • Satisfaction with AR101 treatment as assessed by the TSMQ-9 questionnaire and additional questions
Statistical Considerations	Because enrollment in this study depends upon completion of Study ARC003, sample size will be determined by subject interest in continuing to receive AR101. The sample size for ARC004 is thus based on that of ARC003, which had a target N of 500 and a 3:1 AR101: placebo randomization ratio, providing 89% power to rule out a treatment difference (AR101 minus placebo) of 15% or less at the primary endpoint of the proportion of subjects who tolerate ≥ 1043 mg cumulative of peanut protein with no more than mild symptoms at the Exit DBPCFC. Accrual of 80% of the total ARC003 sample into ARC004 would provide an 80% probability of observing ≥ 1 AE when the background rate of the AE is 4 per 1,000 subjects. No prospective power calculation for efficacy has been made in ARC004. Data will be summarized using descriptive statistics within treatment group and cohort. No specific hypothesis testing or comparisons between the treatment groups is planned for this study. Further details on the analytical approach and exploratory comparisons across cohorts will be provided in the statistical analysis plan (SAP).

Initial Escalation Schedule (Group 1 only)		
Day 1 Dose Number	**AR101 Dose, mg**	**Cumulative AR101 Dose, mg**
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12
Day 2 Dose Number	**AR101 Dose, mg**	**Cumulative AR101 Dose, mg**
1	3	3

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 ≥ 3 mg on Day 1 will return on Day 2 to receive a 3-mg single dose.

Day 2: Subjects with either no symptoms or mild symptoms on Day 2 at 3 mg will start daily home dosing at 3 mg on Day 3.

Subjects with moderate or severe symptoms at 3 mg on either Day 1 or Day 2 will be considered escalation failures.

Up-dosing and Maintenance Schedule (Group 1 only)			
Dose Number	**AR101 Dose, mg**	**Interval (weeks)**	**Percent Increase from Previous Dose**
1	3	2*	n/a
2	6	2	100
3	12	2	100
4	20	2	67
5	40	2	100
6	80	2	100
7	120	2	50
8	160	2	33
9	200	2	25
10	240	2	20
11	300	2	25

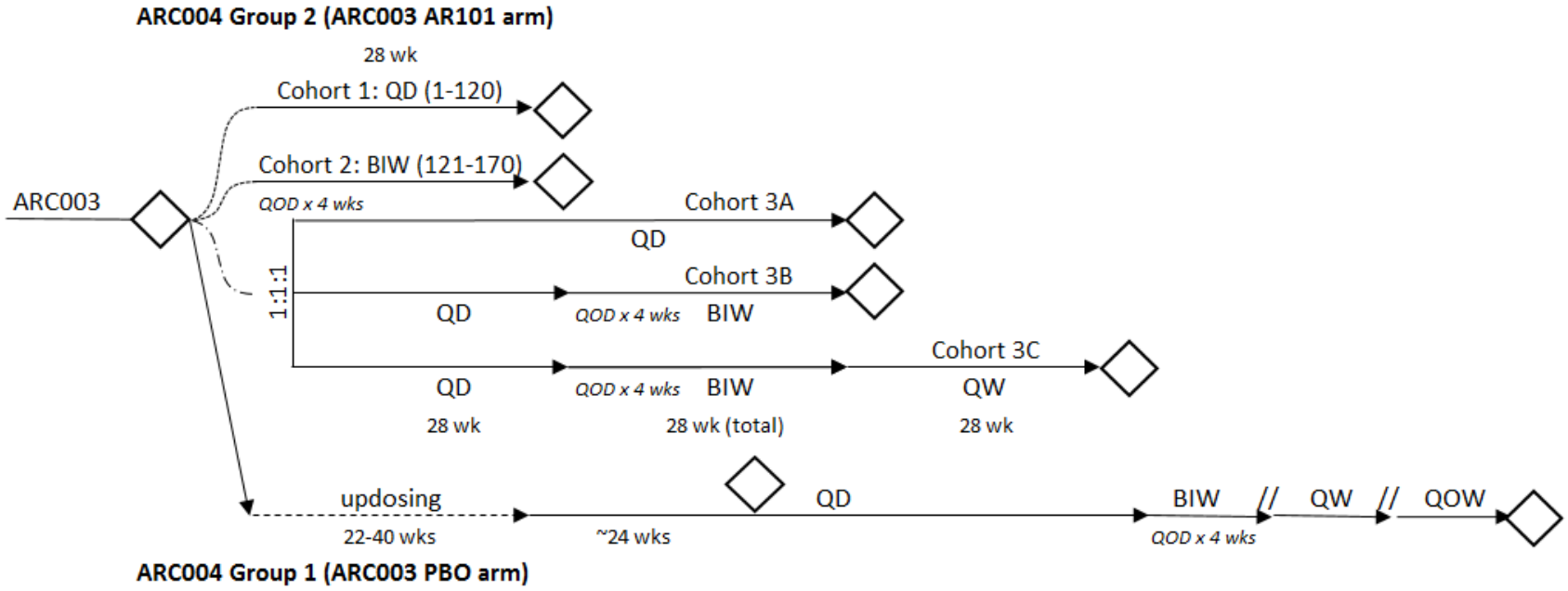
*Interval includes Day 2 of Initial Escalation.

Repeat Up-dosing Schedule (Subjects Switching to Daily Dosing)	
Investigational Product Dose, mg[a]	**Interval (weeks)**
80	2
120	2
160	2
200	2
240	2
300	2

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

DBPCFC Schedule (Post-Maintenance: Group 1 only; Post-Extended Maintenance: Groups 1 and 2)	
Challenge Dose, mg	**Cumulative Dose, mg**
3	3
10	13
30	43
100	143
300	443
600	1043
1000	2043
2000	4043

Figure 1: Study Schematic



Diamonds represent DBPCFCs; all challenges in ARC004 will be to a total of 4043 mg cumulative peanut protein, according to the table above.
The initial ARC004 DBPCFC for Group 1 will be completed after approximately 24-week maintenance period
QD = daily, QOD = every other day, BIW = twice weekly, QW = once weekly, QOW = every other week
NOTE: The BIW interval begins with 4 weeks of QOD dosing before transitioning to 24 weeks of BIW dosing, as tolerated
Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting enzyme inhibitors
ACT	Asthma Control Test
AE	adverse event
AEI	adverse event of interest
AR101	characterized peanut allergen
ARB	angiotensin-receptor blocker
BA/BE	bioavailability/bioequivalence
BIW	twice weekly
BP	blood pressure
CBC	complete blood cell count
CFR	US Code of Federal Regulations
CODIT™	Characterized Oral Desensitization Immunotherapy™
CoFAR	Consortium of Food Allergy Research
CRC	clinical research center
CRF	case report form
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
EAACI	European Academy of Allergy & Clinical Immunology
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
EM	extended maintenance
EoE	eosinophilic esophagitis
FAIM	food allergy independent measure
FAQLQ	food allergy related quality of life questionnaire
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second (spirometry)
GCP / cGCP	Good Clinical Practice / Current Good Clinical Practice
GI	gastrointestinal
HPLC	high-performance liquid chromatography
ICS	inhaled corticosteroids
ICH	International Council for Harmonisation
ICON	International consensus on anaphylaxis
IgE	immunoglobulin E
IgG	immunoglobulin G
IM	intramuscular
IND	Investigational New Drug (application)
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IXRS	Interactive web-based response system

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHLBI	National Heart, Lung, and Blood Institute
OFC	oral food challenge
OIT	oral immunotherapy
PEESS	Pediatric Eosinophilic Esophagitis Symptom Scores
PEFR	peak expiratory flow rate
PR	pulse rate
PRACTALL	PRACTical issues in ALLergology Joint United States/European Union Initiative
QD	once daily
QOD	every other day
QoL	quality of life
QOW	every other week
qPCR	quantitative polymerase chain reaction
QW	once weekly
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SCIT	subcutaneous immunotherapy
SMC	Safety Monitoring Committee
SPT	skin prick test
SUSAR	suspected unexpected serious adverse reaction
SVM	support vector machine
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication Version 9
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 associated with severe reactions, including life-threatening anaphylaxis. Furthermore, the prevalence of peanut allergy, like other food allergies, has been rising, and is now at high levels, affecting up to 1.5% of the population (Branum et al, 2008; Sicherer and Sampson, 2014). The current standard of care in management of peanut allergy is a peanut-avoidant diet, along with education of the patient and family in the acute management of an allergic reaction, including ready access to self-injectable epinephrine. The burden of avoidance and the constant fear of accidental exposure negatively affect the health-related quality of life (QoL) for patients and their families (Primeau et al, 2000; Avery et al, 2003; Buchanan et al, 2007; Sicherer et al, 2010; Hofmann et al, 2009; Anagnostou, 2014).

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

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

There is evidence that OIT induces a clinically meaningful level of desensitization in most subjects and may also induce favorable immunologic changes over time. Though these studies used different doses and regimens, they collectively provide supportive evidence for the efficacy and safety of peanut OIT and were the basis for the initiation of clinical development of AR101, a well-characterized oral desensitization immunotherapy investigational product that is manufactured under current Good Manufacturing Practice (cGMP) and previously tested in Aimmune's Phase 2 program.

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

1.2 Clinical Trials of AR101

1.2.1 ARC001

ARC001 was a phase 2, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic children and adults 4 to 26 years of age. ARC001 consisted of a screening period (including a screening double-blind, placebo-controlled food challenge [DBPCFC]), an initial escalation period, an up-dosing period, and a maintenance period, followed by an exit DBPCFC. The primary endpoint of ARC001 was the percentage of desensitization responders, defined as subjects tolerating 300 mg of peanut protein (443 mg cumulative) at the exit DBPCFC.

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

In the ITT population, AR101 was significantly superior to placebo, with 23 of 29 (79%) desensitization responders as compared to 5 of 26 (19%) desensitization responders in the placebo group, resulting in a treatment difference of 60% ($p < 0.0001$ by Fisher exact test). In the completer population (those subjects reaching the exit DBPCFC), 23 of 23 AR101 completers were desensitization responders, resulting in a treatment difference of 81% ($p < 0.0001$ by Fisher exact test).

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

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

1.2.2 ARC002

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

Group 1 included subjects who completed the placebo arm of ARC001 and consented to enroll in ARC002, crossing over to active treatment using the same dosing regimen used in ARC001, but in open-label fashion. After completion of the buildup phase, Group 1 subjects underwent a DBPCFC (to a maximum single dose of 600 mg of peanut protein, or 1043 mg of cumulative peanut protein). Subjects who did not tolerate the post-low-dose buildup phase DBPCFC at ≥ 443 mg were considered escalation failures and were discontinued from the study for safety considerations. Those subjects who tolerated the DBPCFC at ≥ 443 mg of peanut protein entered an approximately 3-month (12- to 24-week) plateau phase of continued dosing at 300 mg/d. Group 2 subjects completed the active AR101 arm of ARC001 and consented to enroll directly into the 300 mg/d, 3-month plateau phase of ARC002. Following completion of the 3-month plateau phase, subjects underwent a post-plateau phase DBPCFC (to a maximum single dose of 1000 mg of peanut protein, or 2043 mg cumulative).

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

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

1.2.3 ARC003

ARC003 is an international, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in a characterized desensitization OIT regimen in peanut-allergic individuals. The study consists of a screening phase that includes a screening DBPCFC, and a double-blind OIT treatment phase that includes an initial escalation period, an up-dosing period, and a maintenance period, followed by an exit DBPCFC.

All eligible subjects will receive escalating doses of either AR101 or placebo. A DBPCFC will be performed for those subjects achieving the target dose of 300 mg/d and continuing to receive that dose throughout the maintenance period (~24 weeks). Subjects who do not reach

300 mg/d will be considered escalation failures and nonresponders for the primary analysis. Each subject will be unblinded when he/she completes the DBPCFC at the end of the approximately 24-week maintenance period and all major data queries for the subject have been resolved. Those who do not pass the DBPCFC at ≥ 443 mg cumulative challenge dose level will be considered endpoint failures and nonresponders for the primary analysis.

1.3 Rationale for the Current Study

ARC004 is designed as a follow-on study of ARC003. The study population will therefore be based on the ARC003 study population: approximately 500 international peanut-allergic children and adults (ages 4 to 55 years, inclusive). Three main considerations inform the design of the current study ARC004. The first is to allow placebo-treated subjects from ARC003 to have the opportunity to access active treatment with AR101. The second is to prolong treatment periods with AR101 in order to continue assessment of its safety and efficacy profile. Finally, ARC004 is specifically designed to begin exploring alternate (eg, nondaily) OIT extended maintenance dosing regimens. Because no previous peanut OIT studies have formally examined nondaily dosing intervals, no published preliminary data exist to provide guidance. Therefore, the data generated in ARC004 are expected to be exploratory and hypothesis-generating, and to have the potential to shape a larger subsequent study to confirm the observations made in ARC004 of nondaily dosing regimens.

The rationale for extending the interval between OIT doses is primarily derived from the roughly 100 years of accumulated clinical expertise with subcutaneous immunotherapy (SCIT), as encoded in the current SCIT practice parameter documents (Cox et al, 2011). Patients taking SCIT for environmental and/or Hymenoptera venom allergies are conventionally started on schedules that begin, in the up-dosing phase, with doses administered once or twice per week, or in some cases even more frequently (eg, “rush” or “cluster” immunotherapy). As patients become hyposensitized and achieve their target maintenance dose, the intervals between injections are then lengthened to monthly during the maintenance period, with no loss of clinical efficacy or increase in AEs. In turn, this conventional monthly maintenance schedule lessens the substantial logistical and economic burdens on patients and families and helps to ensure long-term adherence. While adherence to therapy is important in all disease contexts, it is especially critical in immunotherapy, a modality that requires periodic antigen administration over the span of years to reprogram immune responses and clinically improve chronic conditions.

By contrast, there is little to no evidence from food immunotherapy studies to determine what effects, if any, the alteration of OIT dosing schedules would have on peanut-allergic individuals and families. ARC004 is one of the first studies to address this question. In contrast to the SCIT experience, when intervals between doses can be safely lengthened once participants achieve the completion of the up-dosing period, all peanut OIT studies published to date have continued daily dosing. Given the absence of data to suggest otherwise, it has been an accepted convention that subjects must take their doses every day unless doing so would create undue risk (eg, in the presence of an intercurrent viral infection, which has been shown to lower thresholds for allergic reactions). This historical convention also informed the AR101 Phase 2 program, in which all doses were intended to be administered daily.

Nonetheless, the Phase 2 protocols allowed for dose to be withheld for up to 3 days, or more as necessary, at the discretion of the investigator due to the presence of intercurrent illness. This provides some preliminary clinical evidence that dosing need not necessarily occur daily to maintain the level of desensitization.

Furthermore, published work from Dr. A. Wesley Burks' research group suggests that 2 to 5 years of peanut OIT can lead to mechanistic changes and "sustained unresponsiveness," allowing safe consumption of 5 grams of peanut protein after a 1-month hiatus from dosing (Vickery et al, 2014; Vickery et al, 2016). Yet preliminary unpublished evidence suggests that even after as little as 6 months of OIT treatment (ie, only the up-dosing phase and a brief maintenance period), subjects may tolerate peanut exposures spaced 1 or more weeks apart (personal communication, A.W. Burks). If true, this would suggest that, once desensitized, exposures to therapeutically administered peanut allergens need not occur every day, as has already been shown for milk (Pajno et al, 2013) and, as described above, Hymenoptera.

The exit DBPCFC of ARC004 will include a final dose of 2000 mg of peanut protein (up to a cumulative dose of 4043 mg). Phase 2 results and peer-reviewed studies published in the medical literature indicate that subjects tolerating a maintenance dose of 300 mg of peanut protein for 6 months are able to tolerate higher amounts of peanut protein during the exit challenge (Jones et al, 2009; Vickery et al, 2017).

It has been previously observed that AR101 was well tolerated and appeared to reproducibly induce desensitization to peanut when used daily. The goal of ARC004 is to examine whether intermittent dosing of AR101 during extended maintenance can preserve the desensitization gained by daily dosing; and if so, how much daily treatment is advisable before the interval can be adjusted. In the short term, the data gained from this study should provide very practical guidance to assist physicians in determining how to manage short-term dosing interruptions. Longer term, the results will have key implications for designing maintenance therapy regimens in future AR101 development protocols.

1.4 Known and Potential Risks and Benefits of AR101

1.4.1 Risks

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

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

esophagitis (EoE), affecting an estimated 3 to 4% of OIT recipients (Lucendo et al, 2014), which is thought to be reversible upon 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 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 (IM), or intravenous (IV) 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 was < 0.1%, and none were seen during food challenges in the Phase 2 program.

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

1.4.2 Benefits

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

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

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the safety, tolerability, and efficacy of AR101 characterized oral desensitization immunotherapy (CODIT^{TM}) using alternative maintenance dosing intervals.

2.2 Secondary Objectives

The secondary objectives are:

- To confirm the safety profile of AR101 as measured by the incidence of AEs, including SAEs
- To confirm the efficacy of AR101 through reduction in clinical reactivity, measured in a DBPCFC to a cumulative dose of 4043 mg
- To evaluate subjects' QoL and treatment satisfaction during AR101 treatment on daily and nondaily treatment regimens
- To evaluate the long-term immunologic effects of AR101 treatment

3 STUDY DESIGN

This is an international, multicenter, open-label, 2-arm follow-on study of ARC003. The 2 arms to be studied in ARC004 are the subjects who received placebo in ARC003 (Group 1) and those who received AR101 in ARC003 (Group 2).

Group 1 (Placebo Crossovers): Subjects who complete the placebo arm of ARC003 are eligible to enroll in ARC004. All placebo subjects who consent to participate in ARC004 will enter Group 1 and will undergo initial escalation, up-dosing, and maintenance with AR101, as in the active arm of ARC003. The Initial Escalation Period consists of a step-wise dose-escalation from 0.5 to 3 or 6 mg (as tolerated) on Day 1 and confirmation of the ability to tolerate a single dose of 3 mg on Day 2. The Up-dosing Period is 22 to 40 weeks in duration and consists of dose escalations every 2 weeks up to a maximum of 300 mg/d (as tolerated). The Maintenance Period consists of daily dosing at 300 mg/d for approximately 24 weeks, at which point Group 1 subjects will undergo a DBPCFC to a maximum total of 4043 mg cumulative peanut protein to test the efficacy of AR101 in desensitizing ARC003 placebo crossovers to large amounts of peanut protein after 6 months of daily maintenance.

All Group 1 subjects tolerating ≥ 443 mg of cumulative peanut protein in this challenge will be eligible to continue in ARC004, and enter the Extended Maintenance (EM) Period, initially consisting of ongoing daily maintenance therapy at 300 mg/d. Dependent upon the EM results from ARC004 Group 2 (below), subjects in Group 1 EM will test the gradual lengthening of their dosing interval from once daily (QD) to every other day (QOD), twice weekly (BIW), once weekly (QW), and finally every other week (QOW), as tolerated. The length of each interval will be between 8 and 24 weeks and will be adjusted based on the data from Group 2. Lengthening to each level will occur sequentially (QD then QOD then BIW then QW and finally QOW), and only if sufficient evidence exists, based on the analyses of the Group 2 EM subjects and the ongoing safety of Group 1 subjects, to support progression to each level.

Group 2 (Active Rollovers): Subjects who complete the active arm of ARC003 and tolerate a challenge dose of ≥ 443 mg cumulative of peanut protein at the ARC003 Exit DBPCFC are eligible to enroll in ARC004. Group 2 subjects will have undergone the Initial Escalation,

Up-dosing, and Maintenance Periods in ARC003 and will therefore enter the ARC004 EM period directly.

Upon entry into the EM phase of the study, Group 2 subjects will be consecutively enrolled into 1 of several cohorts that will conditionally explore an alternate dosing interval regimen over 28-week study periods, as follows:

1. EM Cohort 1: The first 120 Group 2 subjects to enter ARC004 will comprise Cohort 1, and will continue 300 mg of AR101 QD for 28 weeks before undergoing an Exit DBPCFC (total 28 weeks).
2. EM Cohort 2: The next 50 Group 2 subjects (subjects 121-170) enrolling in ARC004 will comprise Cohort 2 and will take 300 mg of AR101 QOD for 4 weeks and then BIW (eg, Monday/Thursday) for 24 weeks (total of 28 weeks) as tolerated, before undergoing an Exit DBPCFC.
3. EM Cohort 3: All remaining subjects recruited into ARC004 (subjects 171 to the end) will comprise Cohort 3. This cohort will be randomized 1:1:1 to 1 of 3 initial strategies:
    a. 300 mg QD for 56 weeks followed by an Exit DBPCFC (Cohort 3A) (total 56 weeks)
    b. 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks, as tolerated, followed by an Exit DBPCFC (Cohort 3B) (total 56 weeks)
    c. 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks, then 300 mg QW for 28 weeks, as tolerated, followed by an Exit DBPCFC (Cohort 3C) (total 84 weeks)

In ARC004, Exit DBPCFCs will test to a maximum of 4043 mg cumulative peanut protein to determine the continued efficacy of each alternate dosing schedule. Following the end-of-study visit, each subject's participation in ARC004 ends. The end of the study is defined as the date of the last visit of the last subject.

End of Participation in ARC004 and Entry into ARC008: After the end of participation in ARC004, subjects may enroll in the long-term, open-label extension study ARC008 to continue treatment with AR101 at their current dosing regimen (QD, BIW, QW, or QOW) or switch to AR101 daily dosing, until AR101 becomes commercially available or ARC008 is terminated, as follows:

- Subjects on any dosing regimen able to tolerate at least the 600 mg single dose of peanut protein (≥ 1043 mg cumulative) at their ARC004 Exit DBPCFC will continue their current dosing regimen in Treatment Pathway 1 of ARC008 when that study is available. If ARC008 is not available at the study site, these subjects may continue their current dosing regimen and have visits in ARC004 until they can enroll in ARC008.
- Subjects who tolerate their alternate (eg, nondaily) dosing regimen and tolerate at least the 300 mg single dose of peanut protein (≥ 443 mg cumulative) but are unable to tolerate the 600 mg single dose of peanut protein (1043 mg cumulative) at the ARC004 Exit DBPCFC will switch to daily dosing with 300 mg AR101 in Treatment Pathway 1 of ARC008, per investigator discretion. If ARC008 is not available at the

study site, these subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.

- Subjects on a nondaily dosing regimen who tolerate less than the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC may be eligible for treatment in ARC008 per investigator judgment and after discussion with the medical monitor. If continued treatment with AR101 is determined to be safe, these subjects will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not yet available or able to accept these subjects at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.
- Subjects who do not tolerate their nondaily dosing regimen (Section 7.8.2) will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.
- Subjects on a nondaily dosing regimen who miss or withhold their dose for > 3 days, including subjects receiving QOD, BIW, or QW dosing who miss or withhold their dose for > 14 days, will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.

Subjects are **not** eligible to enroll in ARC008 when continued treatment with AR101 is determined to be unsafe as follows:

- Subjects on a daily dosing regimen who are unable to tolerate at least the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC.
- Subjects not tolerating their nondaily dosing regimen (Section 7.8.2) who begin Repeat Up-dosing in ARC004, but are unable to dose escalate to AR101 300 mg daily and tolerate that dose level for 2 weeks within 26 weeks.

3.1 Study Periods

The ARC004 study consists of 4 study periods:

- Initial Escalation - Group 1 only
- Up-dosing - Group 1 or Repeat Up-dosing for subjects switching to a daily AR101 dosing regimen (Section 3) at a study site that has not yet received approval to enroll these subjects in ARC008

- Maintenance - Group 1 and subjects switching to a daily AR101 dosing regimen and who completed Repeat Up-dosing at a study site that has not yet received approval to enroll these subjects in ARC008
- Extended Maintenance - Groups 1 and 2

3.1.1 Initial Escalation (Group 1 Only)

All Initial Escalation doses will be administered by investigational site personnel under direct observation. Eligible subjects will initiate treatment with AR101 on Day 1, starting at a dose of 0.5 mg, increasing the dose at 20 to 30 minute intervals to a maximum dose of 6 mg (Table 1). Subjects who fail to tolerate ≥ 3 mg dose on Day 1 will be considered escalation failures and will be discontinued. Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on Day 2. Subjects who do not tolerate this confirmatory dose will be discontinued. Subjects who tolerate this confirmatory dose will enter the Up-dosing Period.

Table 1: Initial Escalation Schedule (Group 1 Subjects Only)

Initial Escalation Schedule (Group 1 only)		
Day 1 Dose Number	**AR101 Dose, mg***	**Cumulative AR101 Dose, mg**
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12
Day 2 Dose Number	**AR101 Dose, mg**	**Cumulative AR101 Dose, mg**
1	3	3

*All mg doses shown refer to milligrams of peanut protein.

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 ≥ 3 mg on Day 1 will return on Day 2 to receive a 3-mg single dose.

Day 2: Subjects with either no symptoms or mild symptoms on Day 2 at 3 mg will start daily home dosing at 3 mg on Day 3.

Subjects with moderate or severe symptoms at 3 mg on either Day 1 or Day 2 will be considered escalation failures.

3.1.2 Up-dosing (Group 1 Only)

Subjects will receive AR101 starting at a dose of 3 mg once daily and gradually escalating every 2 weeks to a maximum of 300 mg once daily, according to the Up-dosing Maintenance

Schedule (Table 2). All escalation doses will be administered under direct observation; subsequent doses will be dispensed to the subject/guardian and administered at home. Doses may be adjusted for tolerability or intercurrent illness; the Up-dosing period may thereby be extended to a maximum of 40 weeks. Subjects unable to escalate to 300 mg within 40 weeks will be considered escalation failures for analysis purposes. Subjects able to escalate to 300 mg and maintain this dose regimen for 2 weeks will have completed Up-Dosing and will enter the Maintenance Period.

Table 2: Up-dosing Maintenance Schedule (Group 1 Subjects Only)

Up-dosing and Maintenance Schedule (Group 1 only)			
Dose Number	**AR101 Dose, mg**	**Interval (weeks)**	**Percent Increase from previous dose**
1	3	2[a]	n/a
2	6	2	100
3	12	2	100
4	20	2	67
5	40	2	100
6	80	2	100
7	120	2	50
8	160	2	33
9	200	2	25
10	240	2	20
11	300	2	25

[a] Interval includes Day 2 of Initial Escalation.
n/a = not applicable.

3.1.3 Repeat Up-dosing (Subjects Switching to Daily Dosing)

If a subject meets the criteria for switching to AR101 daily dosing and is at a study site that has not yet received approval to enroll these subjects in ARC008, the subject may begin daily dosing and have visits in Repeat Up-dosing in ARC004 until they can enroll in ARC008 (Section 3). If ARC008 is available, the subjects will complete an Exit/Early Discontinuation visit in ARC004 and enroll in ARC008.

Subjects entering the Repeat Up-dosing Period will start with a daily dose of either 80, 120, or 160 mg at the discretion of the investigator. The dose will be increased every 2 weeks as per Table 3, until the subject reaches the target dose of 300 mg daily.

To escalate to the next dose, subjects must be tolerating the current dose. Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt to proceed with up-dosing. To allow for a personalized titration of dosing, the Repeat Up-dosing Period will last for a maximum of 26 weeks. Subjects who are not able to achieve the target dose of

300 mg/day and tolerate that dose level within 26 weeks will be discontinued from AR101 dosing and complete an Early Discontinuation Visit; these subjects will not be eligible to participate in ARC008.

Subjects who reach the target maintenance dose of 300 mg and maintain this dose for at least 2 weeks (maximum duration of Repeat Up-dosing of 26 weeks) will exit ARC004 and enter ARC008 when it is available. If ARC008 is not available at the time the subject expects to exit ARC004, subjects will continue daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.

Table 3: Repeat Up-dosing Schedule (Subjects Switching to Daily Dosing)

Repeat Up-dosing Schedule (Subjects Switching to Daily Dosing)	
Investigational Product Dose, mg[a]	**Interval (weeks)**
80	2
120	2
160	2
200	2
240	2
300	2

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

3.1.4 Maintenance

Subjects entering the Maintenance Period will continue AR101 300 mg once daily, undergoing directly observed dosing at 12 and 24 weeks. Down-dosing may be necessary during the Maintenance Period due to safety or tolerability reasons, but such subjects will remain in the Maintenance Period even if they are temporarily taking a dose of less than 300 mg. The duration of the Maintenance Period does not reset if this occurs. After approximately 24 weeks of daily AR101 treatment at 300 mg in the Maintenance Period, Group 1 subjects will undergo a Post-Maintenance DBPCFC with a maximum dose of 2000 mg of peanut protein (4043 mg cumulative), according to the DPBCFC Schedule (Table 4). Subjects who do not tolerate ≥ 300 mg peanut protein (443 mg cumulative) will be considered treatment failures and will be discontinued. Subjects who tolerate ≥ 300 mg peanut protein (443 mg cumulative) will enter the EM and continue taking 300 mg/d of AR101 until the results of the alternate regimens explored in Group 2 subjects are known.

Table 4: DBPCFC Schedule (All Time Points)

DBPCFC Schedule (All Time Points)	
Challenge Dose, mg	**Cumulative Dose, mg**
3	3
10	13
30	43
100	143
300	443
600	1043
1000	2043
2000	4043

3.1.5 Extended Maintenance

The EM periods will differ between and within the 2 groups in duration and dosing regimen (see below and Figure 1). However, all EM subjects who complete their dosing regimen, regardless of group or cohort assignment, will have an Exit DBPCFC up to a single highest dose of 2000 mg of peanut protein (4043 mg cumulative).

Group 1

All Group 1 subjects who tolerate ≥ 443 mg cumulative peanut protein in the Post-Maintenance DBPCFC will enter the EM period. Subjects who do not tolerate ≥ 443 mg are not eligible to continue for safety reasons. The EM period for Group 1 subjects will initially consist of QD dosing while the Group 2 cohorts are undergoing evaluation as outlined below. Conditional upon the safety and DBPCFC outcomes assessed in the Group 2 participants, Group 1 subjects may have their dosing interval serially lengthened from QD to QOD, QOD to BIW, BIW to QW, and QW to QOW, as tolerated. The duration of each of these interval extension periods will be adjusted, based on Group 2's experience, from between 8 to 28 weeks, as tolerated. In clinic visits during the EM for Group 1 subjects will continue to occur every 14 weeks. Following the completion of the longest tested dosing interval, Group 1 subjects will then undergo an Exit DBPCFC and ARC004 will conclude.

Group 2

As they enter ARC004, Group 2 subjects will be consecutively assigned to 1 of 3 cohorts and continue to receive AR101 in the following fashion:

- The first 120 Group 2 subjects (ie, 1 to 120) entering ARC004 will form Cohort 1 and continue to receive QD treatment for 28 weeks as tolerated and then undergo an Exit DBPCFC.

- The next 50 Group 2 subjects (ie, 121 to 170) entering ARC004 will form Cohort 2, receiving AR101 300 mg QOD for 4 weeks, and then BIW for 24 weeks, as tolerated, and then undergoing an Exit DBPCFC.
- All remaining Group 2 subjects (ie, 171 to end) entering ARC004 will form Cohort 3. Upon entering Cohort 3, these subjects will be randomized 1:1:1 to receive AR101 in 28 week periods, as follows. Cohort 3A will receive 300 mg QD for 56 weeks as tolerated and then undergo an Exit DBPCFC. Cohort 3B will receive 300 mg QD for 28 weeks and then 300 mg QOD for 4 weeks followed by BIW for 24 weeks, as tolerated, and then undergo an Exit DBPCFC. Cohort 3C will receive 300 mg QD for 28 weeks, 300 mg QOD for 4 weeks followed by BIW for 24 weeks, and then 300 mg QW for 28 weeks, as tolerated, and then undergo an Exit DBPCFC.

Throughout ARC004 EM, the first 2 doses at extended nondaily dosing intervals (BIW, QW, QOW) will always be administered under direct supervision in the clinic; QOD dosing is an exception and can be initiated at home. Thereafter, the doses will be administered at home as tolerated, and recorded in the subject diary. Investigators may, at their discretion, bring subjects back to the research unit for an observed dose at any time. All AR101 doses will be judged by the investigator to be tolerated or not tolerated according to criteria previously established in ARC003 and specified in Section 6.5.2.

Dosing intervals should be as consistent as possible, preferably on the same days each week.

- In the BIW group, doses should be at least 3 days apart (eg. Monday and Thursday each week)
- In the QW group, doses should be taken on the same day (± 1 day) each week
- In the QOW group, doses should again be taken on the same day (± 2 days), every other week

Any subject receiving nondaily dosing (QOD, BIW, QW, or QOW) who has 1 related SAE; 1 related AE graded severe; 2 related AEs occurring on separate occasions, both graded moderate; or 3 consecutive doses judged “not tolerated,” will be considered a treatment failure in the statistical analysis of each cohort. These subjects will be returned to a 300-mg daily regimen by entering the Repeat Up-dosing period. For the majority of subjects, Repeat Up-dosing will be carried out in Treatment Pathway 2 of ARC008. However, if ARC008 is not available at the study site, subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.

No subject will be exposed to a longer dosing interval if evidence from previous cohorts suggests that doing so would more likely than not cause the subject to either experience more frequent or more severe AEs, or lose desensitization that he or she may have gained/maintained, compared to more frequent dosing. Because subjects in Cohorts 3B and 3C will have had 28 additional weeks of QD maintenance treatment, these subjects will be allowed to proceed to QOD and BIW dosing independent of Cohort 2’s experience according to the judgment of the Safety Monitoring Committee (SMC).

Aimmune will monitor the safety and efficacy in each of the cohorts in accordance with internal procedures and escalate to the internal Safety Monitoring Committee (SMC) for review and recommendation for action. Only when sufficient efficacy and safety evidence is available on a cohort, will the SMC recommend that the next cohort advance to a longer interval between doses. Therefore, only after the safety and efficacy data from Group 2 cohorts are available, reviewed, and approved by the SMC, will the SMC allow the Group 1 patients to modify their once-daily regimen.

For more information on individual-, cohort-, and study-stopping rules, see Section 7.8.

Down-dosing may be necessary during the Extended Maintenance Period due to safety or tolerability reasons; however subjects who had to be down-dosed remain in the Extended Maintenance Period during the dose adjustment. The duration of the Extended Maintenance Period does not reset if this occurs.

Early Discontinuations

Subjects who are discontinued and who do not enter ARC008 will be followed for safety for a minimum of 30 days after the last dose of AR101, 2 weeks after the last food challenge, or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is longer. In addition, subjects who are discontinued from further AR101 dosing due to chronic or recurrent GI AEs will have experienced an AE of interest (AEI) and will be followed monthly for a minimum of 6 months, or until resolution or stabilization of all GI AEs (Section 7.3.3.2 for more information about GI AEIs).

For subjects who do not tolerate their nondaily dosing regimen and subjects who switch to daily dosing after missing their nondaily dose for > 3 days, the exit DBPCFC will be omitted before discontinuation from ARC004 and enrollment in ARC008.

Subjects who are discontinued will not be replaced.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible:

1. Completion of ARC003
2. Written informed consent and/or assent from subject/guardian as appropriate
3. Use of effective birth control by female subjects of child-bearing potential (Section 7.7.3.2)

4.2 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible:

1. Early discontinuation from ARC003

2. Meets any longitudinally applicable ARC003 exclusion criteria (Appendix 7)
3. (Group 2 only) Failure to tolerate 443 mg cumulative of peanut protein with no or mild symptoms in the ARC003 Exit DBPCFC
4. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety

4.3 Early Termination

4.3.1 Criteria for Early Termination

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

1. Life-threatening symptoms (Consortium of Food Allergy Research [CoFAR] Grade 4; refer to Appendix 4), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
2. Severe allergic hypersensitivity symptoms (CoFAR Grade 3; refer to Appendix 4), 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. Subjects who experience severe symptoms (eg, severe nausea, rhinorrhea, or pruritus) that are not life-threatening, not requiring intensive therapy, and not associated with any other features indicating a serious clinical condition, and who the Investigator feels are suitable to continue with the study, will be discussed with the Medical Monitor and may continue the trial under close supervision, if both the Investigator and the Medical Monitor deem it appropriately safe to do so.
3. Pregnancy
4. Non-adherence (non-compliance) with study product dosing, as indicated by missing ≥ 7 consecutive dosing days on any 1 occasion, or 3 consecutive dosing days on 3 or more occasions during the Up-dosing Period, as this could constitute a potential safety issue (QD regimens only)
5. Medically indicated circumstances (eg, as part of the treatment for intercurrent AEs) that require missed study product dosing for >14 consecutive days, except for the voluntary 30-day hiatus for AEs occurring at or before the 20-mg dose (Group 1 only)
6. The subject elects to withdraw consent from all future study activities, including follow-up.
7. The subject is "lost to follow-up" (ie, no further follow-up is possible because attempts to reestablish contact with the subject have failed).
8. The subject's continued participation in the study is assessed by the investigator to constitute a threat to the safety of the subject or the safe conduct of the study.
9. The subject dies (CoFAR Grade 5).

10. Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma)
11. 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
12. The subject develops biopsy-documented eosinophilic esophagitis (EoE)

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

4.3.2 Follow-up of Subjects

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

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

Subjects who discontinue treatment due wholly or in part to GI AEs will be instructed to complete the Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS^{TM} v2.0) questionnaire (Franciosi et al, 2011) monthly for 6 months. These subjects will also be asked to continue to fill out their daily diary for the same 6-month duration. Additional instructions for the follow-up of subjects who discontinue treatment due wholly or in part to GI AEs is contained in Section 7.3.3.2.

4.3.3 Subject Replacement

No subject who is randomized or enrolled in this trial and who undergoes early termination will be replaced.

5 STUDY TREATMENT

5.1 Formulation, Packaging, and Labeling

The active study product AR101 (characterized peanut allergen) is 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, 20, and 100 mg each of peanut protein. Capsules containing study product will be provided in pre-packaged bottles or blister cards assembled into dosing kits for Up-dosing. Each individual bottle or blister of a blister card will contain a single day's dose of study product. For daily dosing regimens, each kit

will contain 21 daily doses at a given dose level, enough to supply 2 weeks of dosing plus a 7-day overage to accommodate potential visit scheduling issues. Kits for nondaily regimens may be modified accordingly and will also contain overages allowing for visit flexibility. For the Maintenance and EM periods, AR101 will be provided in foil-lined sachets at a dose of 300 mg.

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 study products (in blister packets for initial dose escalation and up-dosing and in sachets for maintenance dosing) will then be shipped to a drug depot where they will be labeled and inventoried for shipment to the clinical sites. Study products will be shipped by the drug depot to the investigational site or the investigational site pharmacy, according to site-specific institutional policies. Study products will then be distributed to subjects/subjects' parents or guardians by study site personnel. 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 first dose at each new dose level during the Up-dosing Period, and the first 2 doses at each extended dosing interval regimen (BIW, QW, and QOW) are to be administered in the clinical research center (CRC) under the direct supervision of an appropriately credentialed healthcare provider and the oversight of a physician. Once the dose(s) are removed from a dosing kit for in-clinic administration, the kit must be dispensed to the subject or held at the site for documented destruction or returned to the Sponsor's designee (as instructed); dosing kits once opened cannot be used for any other dosing interval or any other subject. At clinic visits, subjects will receive a kit of capsules/sachets to be taken at home according to their specific dose level. The subjects will be instructed to document capsules/sachets taken at home using subject diary logs and to bring all unused capsules/sachets back to the clinic at the next visit. The subjects will be instructed to store the dosing kit in the refrigerator except when it is removed to obtain the daily dose.

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

Care must be taken not to inhale the powder as this could provoke worsening of asthma or induce an allergic reaction. Study product may not be added to food heated above room temperature before consumption. The vehicle food must be one to which the subject is not additionally allergic. The volume of the vehicle food should be such that the entire dose can

be consumed in a few spoonfuls. The study product should be consumed as promptly after mixing as practicable. If not consumed within 4 hours of mixing in a vehicle, the study product-vehicle food mixture should be discarded and a new dose mixed prior to consumption. If preparing a new dose is not feasible, the study product may be stored for up to 24 hours under conditions appropriate for the food matrix in which the study product was prepared. If there is a delay of more than 24 hours in consumption, the study product is to be discarded and a new study product dose mixed and consumed. It is recommended that each dose of study product be taken at a consistent time (within a 4-hour time period) each day that the dose is to be taken. A target interval of ≥ 8 hours should pass between doses. Per investigator judgment, a home dose may be split into 2 portions for tolerability reasons, further discussed in Section 6.5.5.2.

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

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

For subjects on nondaily EM regimens, doses should be administered at approximately the same time on the scheduled days. If more than 6 hours has elapsed since the dose was due, the dose should be considered missed due to non-adherence, and administered the following day (at approximately the same time of day as previously administered). Thereafter, the subject should return to the original schedule. Please refer to the Study Manual on return to dosing. All administered doses will be entered into dosing logs and reviewed by the site. Missed or withheld doses on nondaily EM schedules due to intercurrent AEs represent a special situation and are discussed further in Section 6.5.7.

5.3 Drug Accountability

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

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

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

5.4 Assessment of Compliance with Study Treatment and Monitoring

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

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

5.5 Modification of Study Treatment

Study product doses may be adjusted by the study physician if the subject is unable to tolerate their scheduled dose level. If such a dose modification occurs requiring dosing at a lower dose level, the subject will return all unused capsules/sachets of study product during a dose adjustment visit, and be dispensed new capsules at the adjusted dose level.

5.6 Concomitant Medications

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

5.7 Prophylactic Medications

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

5.8 Rescue Medications

Treatment of individual acute allergic reactions during ARC004 should be with either an antihistamine and/or epinephrine, along with IV fluids, beta-adrenergic agonist (eg, albuterol), oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely already to have an epinephrine auto-injector device, but for those who do not, an epinephrine auto-injector device will be provided. The expiry dates for the epinephrine

auto-injectors should be tracked by the site and subjects/families resupplied as necessary. Study staff must document in each subject's medical record that the subject and/or parent/guardian have a current unexpired epinephrine auto-injection device and have been trained in its proper usage including injection technique.

5.9 Symptomatic Treatment for Chronic and/or Recurrent Adverse Events

Symptomatic treatment for chronic/recurrent AEs is permitted (except for prohibited medications [Section 5.10]), but should be used to supplement dose reduction, not substitute for it. It is advised that an attempt to withdraw symptomatic therapy be made prior to dose re-escalation. If unsuccessful, symptomatic therapy may be resumed and dose escalation may proceed with the symptomatic therapy in place. However, any therapy instituted for treatment of IgE-mediated AEs related to study product must be withdrawn by 4 weeks prior to the Exit DBPCFC.

5.10 Prohibited Medications

- Therapeutic immunomodulatory antibodies (eg, omalizumab, mepolizumab, reslizumab, etc.)
- 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
- Beta-blockers (oral)
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-receptor blockers (ARB)
- Calcium channel blockers
- Tricyclic antidepressants

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

Immunomodulatory (including immunosuppressive) medications constitute another class of drugs whose use during the course of the study is generally prohibited. It is beyond the scope

of this protocol to list all immunomodulatory drugs; broadly, these include drugs to treat or prevent transplant rejection, autoimmune disease, and certain neoplasias – examples include cyclosporine, tacrolimus, anti-tumor necrosis alpha drugs, and other anti-cytokine drugs. If an investigator contemplates the use of a potentially immunomodulatory drug during the course of the study, the investigator should discuss this with one of the study's Medical Monitors.

6 STUDY PROCEDURES

6.1 Enrollment and Randomization

At ARC003 exit, subjects who have successfully completed the ARC003 study, signed ARC004 informed consent form (and assent, as age-appropriate), and satisfied all ARC004 inclusion/exclusion criteria will be enrolled in ARC004. After obtaining signed ARC004 consent (and assent as appropriate), screening procedures for ARC004 may be initiated. Screening procedures may be performed concurrently with the ARC003 Exit DBPCFC but must be completed prior to a subject's enrollment in ARC004. Procedures that are performed as part of the ARC003 Exit Visit should not be repeated as part of the ARC004 Screening and Baseline Visit. Once the ARC003 Exit DBPCFC procedure is completed, subjects will be unblinded to their ARC003 treatment assignment and their treatment assignment will be verified against the ARC003 unblinded site records prior to enrollment in ARC004. Subjects will be assigned to Group 1 or Group 2 based on their treatment assignment in ARC003 without re-randomization; Group 1 comprising those subjects who were assigned to placebo in ARC003, and Group 2 comprising those subjects who were assigned to active AR101 treatment in ARC003.

Subjects in Group 1, formerly receiving placebo in ARC003, must begin dosing in ARC004 within 10 days of completion of ARC003. No subject in ARC004 should receive AR101 administered on the same day as the ARC003 Exit DBPCFC. Subjects in Group 2 should begin dosing in ARC004 as soon as safe and feasible after their ARC003 Exit DBPCFC, and at maximum within 3 days of completing ARC003. For Group 2 subjects, this first dose can be given at home. If ARC004 dosing for a Group 2 subject does not commence within a 3-day period of completing ARC003, the site should contact the Medical Monitor prior to administering the first dose.

AR101 will be shipped directly to investigational sites and will be dispensed according to subject identification number, using a web-based interactive response system (IXRS). IXRS will also be used to randomize the Cohort 3 subjects into Cohort 3A, 3B, or 3C.

6.2 Screening and Baseline Visit – (Group 1 and Group 2)

All screening procedures for the ARC004 Screening and Baseline Visit should be performed prior to entry in ARC004. Procedures that are performed as part of the ARC003 Exit Visit should not be repeated as part of the ARC004 Screening and Baseline Visit. Subjects should

not dose at home on the day of their ARC003 Exit Visit/ARC004 Screening and Baseline Visit if that visit includes a DBPCFC. The visit will include the following procedures:

- ARC004 informed consent and assent, if not already performed.
- Confirmation of treatment assignment from ARC003, following the completion of the ARC003 Exit DBPCFC.
- Inclusion/exclusion criteria review.
- Medical, allergy, and dietary history.
- Concomitant medications.
- Physical examination, including weight and height.
- Serum pregnancy test for females of childbearing potential.
- Pre-DBPCFC vital signs (BP, pulse rate [PR], body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (forced expiratory volume in 1 second [FEV_1]), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- DBPCFC (Part B of the Exit DBPCFC from ARC003).
- Post-DBPCFC vital signs (BP, PR, body temperature).
- Blood draw to collect samples for:
  - Peanut- and peanut component-specific IgE and IgG4 (immunoglobulin assays). The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
  - Complete blood cell count (CBC), obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Additional blood samples for optional exploratory immunologic studies. These can be obtained at selected centers with the same venipuncture as the blood draw for the immunoglobulin assays (separate informed consent required).
- Optional collection of saliva sample for exploratory biomarker development at selected centers (separate informed consent required), as outlined in Appendix 6. Any subjects who consented to this optional substudy as part of ARC003, Amendment 3, will need to be re-consented to continue participating in ARC004.
- Skin prick test (SPT), if not performed prior to Part A of the ARC003 Exit DBPCFC.

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

6.3 Study Visits

The subsections that follow list the evaluations and procedures required at each study visit. Additionally, Appendix 1 contains the schedules of events for each treatment group as a reference guide. To conserve space some visits are consolidated and some details omitted in the schedule of events. For complete details on individual study visit requirements, please refer to the procedures specified in each subsection.

6.3.1 Initial Escalation: Day 1 (Group 1)

The Initial Escalation Phase Visit for Group 1 subjects will occur within 10 days after the ARC003 Exit/ARC004 Screening and Baseline Visit. If the Initial Escalation is not started in this time frame, written approval to rescreen the subject and/or to waive any of the screening procedures must be obtained from the Sponsor's Medical Monitor.

A physician will be available at all times during the CRC peanut OIT dosing visits. Subjects must be free from active wheezing or a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to initiating study product dose escalation. Additionally, subjects must be fully recovered (ie, back to their baseline state of health) from any preceding illness for ≥ 3 to 7 days, depending on the investigator-determined severity of the illness.

The following assessments/procedures will be performed during the Initial Escalation Day 1 visit in the CRC:

- Concomitant medication update.

- Physical examination, including weight and height.
- Diet (food allergen exposure) history update.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Administration of AR101, with dosing beginning at 0.5 mg and progressing in graduated doses (if tolerated) of 1, 1.5, 3, and 6 mg. Following the first dose, subsequent doses will be delivered at 20 to 30 minute intervals. The schedule for initial day dose escalation is also shown in Table 1.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post-dose, and prior to next dose, and at 30-minute intervals thereafter, if the time between doses is extended, and for the duration of the post-dose observation period.
- Monitoring for AEs, including allergic symptoms (see below and Section 6.5.3.1 and Section 7.2).
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

Subjects may have clear liquids or flavored gelatin (eg, Jell-O®) during the day of the initial day escalation procedure while they are being given the desensitization doses. At a minimum, subjects must be observed for 90 minutes (1½ hours) after completion of dose escalation, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the case report form (CRF) on the appropriate Dosing Symptom/AE form.

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

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

If dose-limiting symptoms occur at or before the 3-mg single dose, there will be no further dosing of study product, and the subject will be classified as an escalation failure and a nonresponder for the purpose of primary and key secondary analyses. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10). Adverse events will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first.

If no dose-limiting symptoms occur during Day 1 dose escalation, or if dose-limiting symptoms occur only with the 6-mg single dose, the subject is to return to the CRC on the following day, Day 2, to confirm the tolerability of a single 3 mg dose of AR101.

6.3.2 Initial Escalation: Day 2 (Group 1)

On Day 2, the next consecutive day following Day 1, a single confirmatory 3-mg dose will be administered under medical supervision in the CRC. The only exception to Day 2 immediately following Day 1 is when unforeseen circumstances (eg, an intercurrent illness) creates a safety risk to provide the next dose, consistent with the rules for missed doses (Section 6.6).

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

The following assessments/procedures will be performed during the Initial Escalation Day 2 visit in the CRC:

- Concomitant medication update.
- Diet (food allergen exposure) history update.
- Symptom-directed physical examination.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

*Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.

- Oral administration of a single 3 mg dose of AR101.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post dose, prior to discharge, and as indicated per investigator discretion during the post-dose observation period. Subjects with moderate or severe symptoms should be monitored every 30 minutes.
- Monitoring for AEs, including allergic symptoms (Section 7).
- Diary review with subject.
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

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

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

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

If dose-limiting symptoms occur on Day 2, there will be no further dosing of AR101, and the subject will be classified as an escalation failure and a nonresponder for the purpose of primary and key secondary analyses. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10). Adverse events will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first.

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

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

6.3.3 Up-dosing/Repeat Up-dosing Visits (Group 1 and Subjects Switching to Daily Dosing)

6.3.3.1 Group 1 Up-dosing

The Up-dosing Period for Group 1 will last approximately 22 (to a maximum of 40) weeks and comprise 11 scheduled up-dosing visits, with the potential for unscheduled visits for assessment of dose tolerability, dose-reduction, dose re-escalation, or management of AEs. Subjects will return to the clinic every 2 weeks for up-dosing to a maximum daily dose of 300 mg. The first dose of study product at each new dose level will be administered in the CRC under direct observation and medical supervision.

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

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

The following assessments/procedures are scheduled for each up-dosing visit in the CRC (except the 80 mg up-dosing visit and end of up-dosing/maintenance visit 1, Section 6.3.4 and Section 6.3.5):

- Concomitant medication review.
- Diet (food allergen exposure) history update.
- Return unused capsules to the clinic at each visit.
- Symptom-directed physical examination.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

*Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.

- Study product administration under observation in the clinic.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post dose, prior to discharge, and at the investigator's discretion during the post-dose observation period.
- Take home capsules for daily dosing until next visit.
- Monitoring for compliance.
- Monitoring for AEs, including allergic symptoms (Section 7.2).
- Diary review with subject.
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.
- Optional saliva collection at selected centers (per the Schedule of Events in Appendix 6).

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

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

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

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

A dose escalation attempt may be postponed 1 to 2 weeks if, in the clinical judgment of the investigator, the current dose level has not been sufficiently well tolerated to proceed to the next dose level. Further, if an investigator suspects that a subject has not tolerated, or is not tolerating, his or her current dose level, the investigator should have the subject return to the clinic to determine whether a dose reduction is warranted, and if so, the magnitude of the

reduction. Guidelines for setting the new, lower, dose are outlined in Section 6.5.5 with the dose adjustment depending on the severity of the dose-related symptoms.

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

Following a dose reduction, it is advised that an escalation attempt be made by 4 weeks, unless escalation is to be delayed further due to administration of epinephrine, as defined in Section 6.5.6. Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced ≥ 2 weeks apart, will result in the cessation of dosing and the subject being considered an escalation failure and nonresponder. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10) and is to be followed for safety in the interim.

6.3.3.2 Repeat Up-dosing (Subjects Switching to Daily Dosing)

Subjects who have the option to switch to AR101 daily in ARC008 may begin daily dosing and have visits in the Repeat Up-dosing Period in ARC004 if ARC008 is not yet available at the study site (Section 3). The procedures to be performed are the same as those listed in Section 6.3.3.1, except that the subjects will start the Repeat Up-dosing Period at 80, 120, or 160 mg dose and escalate from there. Repeat Up-dosing may be up to a maximum of 26 weeks.

6.3.4 80 mg Up-dosing Visit

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

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

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

6.3.5 End of Up-dosing Visit/Start of Maintenance (Group 1 and Subjects Switching to Daily Dosing)

The end of the Up-dosing Period/Maintenance Visit 1 occurs after a subject has maintained the 300 mg dose for approximately 2 weeks. The subject then enters the Maintenance Period and remains in it, even if the dose is adjusted due to adverse events (AEs). At the End of Up-dosing Visit/Maintenance Visit 1, the following procedures are to be performed:

- Concomitant medications.
- Diet (food allergen) history.
- Complete (not just symptom-directed) physical examination, including height and weight.
- Vital signs (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Urine pregnancy test, for females of childbearing potential.
- Blood draw to collect samples for:
  - Immunoglobulin assays (peanut-specific IgE, IgG4). The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
  - Complete blood count, obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Optional blood samples for exploratory immune studies at selected centers. Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an additional volume of blood to be collected. Separate informed consent is required.

  - The amount of blood to be taken in total for the above assays (required immunoglobulin assays, required CBC, and optional exploratory immune studies sample) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.
- Optional saliva collection at selected centers (Appendix 6).
- Skin prick test to peanut extract.
- Administration of OIT at site.
- Diary review with subject.
- Dispense/ return unused study product.
- Monitor AEs/allergic symptoms.
- Monitor for compliance.
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test (ACT).
- Review with subjects and parents or guardians teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):
  - Recognition of an allergic reaction and of the symptoms of anaphylaxis
  - When and how to administer epinephrine via auto-injector
  - Requirement to go to nearest emergency facility following use of epinephrine auto-injector
  - Ways to minimize the risk of accidental exposure to peanut in, and outside of, the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)
- Telephone follow-up.

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

6.3.6 Maintenance Visits (Group 1 and Subjects Switching to Daily Dosing)

The Maintenance Period begins approximately 2 weeks after the subject reaches the 300 mg in-clinic dosing visit. The first in-clinic visit in the Maintenance Period is to occur approximately 2 weeks after the start of dosing at 300 mg/d and is the End of Up-dosing Visit/Maintenance Visit 1. Thereafter, Maintenance Period visits will occur approximately every 12 weeks (e.g., Weeks 12 and 24) prior to the subject entering Extended Maintenance).

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

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

- Concomitant medication review.
- Diet (food allergen exposure) history update.
- Return unused sachets or capsules to the clinic at each visit.
- Symptom-directed physical examination.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test.
- Study product administration under observation in the clinic.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post dose, and at 15- to 30-minute intervals thereafter if the post-dose observation period is prolonged beyond the requisite 30 minutes (see below).
- Take home sachets (or capsules, as appropriate) for daily dosing until next visit.
- Monitoring for compliance.
- Monitoring for AEs, including allergic symptoms (Section 7.2).
- Diary review with subject.
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.
- Telephone follow-up.

In the event that dose reduction from the stable dose of 300 mg/d is required during the last weeks of the planned 24-week Maintenance Period, the Maintenance Period may be extended on an individual basis up to an additional 4 weeks (to a maximum of 28 weeks) or to a maximum study duration of 68 weeks, whichever is shorter. The Post-Maintenance DBPCFC must be performed in Group 1 subjects by Week 68.

If dosing is discontinued, the subject will be asked to return to the CRC 14 days following their last dose of AR101 to undergo an Early Discontinuation Visit (Section 6.3.10).

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

The procedure for monitoring subjects for safety after in-clinic dosing is the same as for up-dosing visits (Section 6.5.3), except that the initial period of required post-dose observation may be shortened to 30 minutes for tolerated doses.

Additional procedures are to be performed before the Post-Maintenance DBPCFC at the end of Initial Maintenance for group 1 subjects only, as follows:

- Blood draw to collect samples for:
  - Immunoglobulin assays (peanut-specific IgE, IgG4). The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
  - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Optional blood samples for exploratory immune studies at selected centers. Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an additional volume of blood to be collected. Separate informed consent is required.
  - The amount of blood to be taken in total for the above assays (required immunoglobulin assays, required CBC, and optional exploratory immune studies sample) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.
- Skin prick test to peanut extract.

6.3.7 Double-Blind, Placebo-Controlled Food Challenge (Groups 1 and 2)

Group 1 subjects will undergo a Post-Maintenance DBPCFC, to be conducted in the same manner as the ARC003 Exit DBPCFC, but with a top dose of 2000 mg (4043 mg cumulative) peanut protein added, as shown in Table 4.

All subjects in Groups 1 and 2 who complete their dosing regimen will undergo an Exit DBPCFC up to a single highest dose of 2000 mg of peanut protein (4043 mg cumulative), according to Table 4. For subjects who do not tolerate their nondaily dosing regimen and subjects who switch to daily dosing after missing their nondaily dose for > 3 days, the Exit DBPCFC will be omitted before discontinuation from ARC004 and enrollment in ARC008. Subjects should not administer their AR101 dose on the day of the DBPCFC. All DBPCFCs will be conducted and evaluated based on PRACTALL guidelines. Sites will be provided a DBPFCFC manual, as in ARC003.

6.3.8 All Subjects (Groups 1 and 2): Extended Maintenance Visits

The EM period begins upon entry in ARC004 for Group 2, and following completion of the Post-Maintenance DBPCFC for Group 1.

6.3.8.1 Alternate Dosing Initiation Visit: Day 1

Subjects in Cohorts 2, 3B, and 3C will change to BIW dosing once they have tolerated QOD dosing for 4 weeks. Subsequently Cohort 3C may extend the interval further. Subjects extending their dosing interval (eg, QOD to BIW, BIW to QW, QW, to QOW) will do so by taking the first 2 doses of the new interval under observation in clinic (except QOD). Every effort should be made to ensure the new interval is the appropriate interval. Some or all of the following procedures may be performed at the first of these 2 visits, according to the procedures outlined in the Schedule of Events:

- Diet (food allergen) history.
- Concomitant medication update.
- Symptom-directed physical examination.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Urine pregnancy test.
- Oral administration of AR101.
- Skin prick test.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post dose, prior to discharge, and as indicated per investigator discretion during the post-dose observation period. Subjects with moderate or severe symptoms should be monitored every 30 minutes.
- Blood draw to collect samples for:
  - Immunoglobulin assays. The amount of blood taken for the immunoglobulin assays will be communicated from the central laboratory and included in the Manual of Procedures.
  - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Optional blood draw for exploratory immune studies at selected centers. Note that these can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays. Separate informed consent is required.

  - The amount of blood to be taken for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.
- Monitoring for AEs, including allergic symptoms.
- Monitoring for compliance.
- Diary review with subject.
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.
- Telephone follow-up.

6.3.8.2 Alternate Dosing Initiation Visit: Day 2

Subjects in the cohorts listed above will return to take their second BIW, QW, or QOW dose under observation in clinic. Procedures performed on Day 2 are a subset of procedures performed on Day 1. The following will also occur at the Day 2 visit: Dispense study drug.

6.3.9 Follow-up Extended Maintenance Visits

The follow-up EM period visits should take place approximately every 14 weeks and occur on a day when the dosing interval is due to be changed and/or the subject is due to take the previously specified dose.

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

Some or all of the following assessments/procedures are scheduled for in-clinic dosing EM period visits in the CRC, according to the Schedule of Events:

- Concomitant medication review.
- Diet (food allergen exposure) history update.
- Return unused sachets or capsules to the clinic at each visit.
- Symptom-directed physical examination.
- Pre-dose vital sign measurement (BP, PR, body temperature).
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician’s discretion. The attempt must be documented, and a clinical assessment is required.

- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test questionnaire.
- Urine pregnancy test.
- Skin prick test at entry into EM and every 28 weeks while on QD treatment; more frequently when on nondaily treatments as per the Schedules of Events (Appendix 1).
- Blood draw to collect samples for:
  - Immunoglobulin assays. The amount of blood taken for the immunoglobulin assays will be communicated from the central laboratory and included in the Manual of Procedures.
  - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Optional blood draw for exploratory immune studies at selected centers. Note that these can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays. Separate informed consent is required.
  - The amount of blood to be taken for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.
- Study product administration under observation in the clinic.
- Post-dose vital sign measurements (BP, PR) within 15 to 30 minutes post dose, and at 15- to 30-minute intervals thereafter if the post-dose observation period is prolonged beyond the requisite 30 minutes (see below).
- Take home sachets for daily dosing until next visit.
- Monitoring for compliance.
- Monitoring for AEs, including allergic symptoms (Section 7.2 and Section 4).
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study and encouraged to call the site with any questions or concerns about the intermittent dosing schedule.

The procedure for monitoring subjects for safety after in-clinic dosing is the same as for up-dosing visits (Section 6.5.3), except that the initial period of required post-dose observation may be shortened to 30 min for tolerated doses.

If dosing is discontinued during the EM period, the subject will be asked to return to the CRC 14 days following his or her last dose of AR101 to undergo an Early Discontinuation Visit (Section 6.3.10).

In addition to in-person clinic visits, sites will contact subjects by telephone periodically during EM to assess ongoing tolerability of doses, adherence to dosing schedule, and assessment of medical history/concomitant medications. All phone contacts are to be documented in the subject source record.

6.3.10 Exit Visit/Early Discontinuation Visit

Subjects who tolerate their EM regimen and complete the EM phase will have an Exit Visit, including an Exit DBPCFC, per Figure 1 and the Schedule of Events (Appendix 1).

Subjects who fail initial escalation or up-dosing, or who prematurely discontinue treatment at any other time during the study, will return to the site for an Early Discontinuation Visit that consists of the same procedures as the Exit Visit, but without a DBPCFC. The Early Discontinuation Visit is to occur 14 days after the last dose of study product for those subjects who will permanently discontinue AR101 treatment.

Subjects who have the option to switch to AR101 daily in ARC008 (Section 3) have 2 options to continue, depending on whether ARC008 is available at their study site. If ARC008 is available, subjects will complete an ARC004 Early Discontinuation Visit without a DBPCFC and enroll in ARC008 where they will undergo Repeat Up-dosing. If ARC008 is not available at the study site, subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.

Once ARC008 is available at the study site, subjects will have their Early Discontinuation Visit within 3 days following their last dose of AR101 in ARC004. The exit DBPCFC will be omitted.

Subjects who withdraw from ARC004 wholly or in part due to intolerable GI symptoms, who are not enrolled in the optional saliva study, may be approached at the time of their Early Discontinuation Visit to provide voluntary consent to enroll and participate in the saliva sub-study. If this occurs, such subjects will provide a saliva sample as part of the Early Discontinuation Visit and then again during post-OIT follow-up (table in Appendix 6).

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

- Concomitant medication review.
- Diet (food allergen) history.
- Completion of the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire after the completion of the Exit DBPCFC.
- Completion of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and the exit questionnaire after the completion of the Exit DBPCFC.
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test questionnaire.
- Complete (not just symptom-directed) physical examination, including height and weight.

- Vital signs (BP, PR, body temperature); if DBPCFC is to be conducted, these vital sign measurements should be taken shortly before the first challenge dose.
- DBPCFC, for ARC004 completers.
- Post-DBPCFC vital signs.
- Peak expiratory flow rate (PEFR), performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit. Three attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age: peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.
- Spirometry* (FEV_1), performed when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination); 3 attempts of FEV_1 should be performed, and the best attempt selected.

  *Only for subjects 6 years of age and older who are able to adequately perform spirometry. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
- Urine pregnancy test, for females of childbearing potential.
- Blood draw to collect samples for:
  - Immunoglobulin assays. The amount of blood taken for the immunoglobulin assays will be communicated from the central laboratory and included in the Manual of Procedures.
  - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays.
  - Optional blood draw for exploratory immune studies at selected centers. Note that these can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays. Separate informed consent is required.
  - The amount of blood to be taken for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. (For subjects who are withdrawing prematurely from the study due to an AE, the blood draw at the Early Discontinuation Visit can be foregone if it was performed at the time that dosing with study product ceased.)
- Skin prick test prior to Part A of the DBPCFC.
- Monitoring for compliance.
- Monitoring for AEs, including allergic symptoms (Section 6.5 and Section 7.2).
- Diary review with subject.
- Optional saliva collection (at selected centers) and PEESS v 2.0 questionnaire, as indicated (Appendix 6), for subjects terminating early where GI AEIs were a contributing factor (Section 7.3.3.2).
- Reminder to continue peanut-avoidant diet.

- Return any unused AR101.
- If the subject is at a study site that has not yet received approval to enroll subjects in ARC008, an additional 14-weeks supply of AR101 may be dispensed to the subject. The subject will return to the study site every 14 weeks for an Unscheduled Visit to obtain additional AR101 supplies and to ensure subject safety until such time that ARC008 is enrolling subjects at the site. Once ARC008 is open to enrollment at the study site, the subject will return to clinic and complete the Early Discontinuation Visit to return any unused AR101.

Eligible subjects at their Exit Visit will have an Exit DBPCFC performed. The Exit DBPCFC is to be conducted in accordance with PRACTALL guidelines, with the protocol-specified modifications, as described in Section 6.3.10.

All ARC004 subjects who tolerate ≥ 443 mg cumulative peanut protein at the Exit DBPCFC are eligible to proceed to Study ARC008. Those on QD dosing at the end of EM who do not pass the Exit DBPCFC at ≥ 443 mg cumulative challenge dose level will be considered endpoint failures and nonresponders for the primary analysis. They will not be eligible for rollover into the ARC008 protocol due to safety concerns.

However, subjects on a nondaily dosing regimen (QOD, BIW, QW, or QOW) who tolerate less than the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC will not necessarily be excluded from ARC008, if otherwise eligible. If continued treatment with AR101 is determined to be safe per investigator judgment and after discussion with the medical monitor, these subjects will have the option to receive AR101 daily in ARC008. If ARC008 is not yet available or able to accept these subjects at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.

6.4 Unscheduled Visits / Unscheduled Blood Draws

The procedures performed at unscheduled visits may include any or all of those performed at Up-dosing, Initial Maintenance, or Extended Maintenance visits, as applicable.

Additionally, if a subject (subject's parent/guardian) declares his or her intention to discontinue study product dosing, whether at a scheduled visit or an unscheduled visit, a blood draw should be performed to obtain a CBC, immunoglobulin assays, and optional exploratory immune cell characterization samples (if the subject is participating in the substudy). If a blood draw is performed at this time, it will take the place of the Exit Visit/Early Discontinuation Visit blood draw (Section 6.3.10).

6.5 Assessment and Treatment of Allergic Reactions to Peanut OIT

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

Subjects may develop allergic symptoms during the course of OIT, similar to those seen during other desensitization protocols (eg, venom immunotherapy, drug desensitization, desensitization to aeroallergens by subcutaneous injection). The severity of the reaction will

be determined based on the investigator's judgment. The following definitions, developed to be consistent both with the PRACTALL consensus report on DBPCFC, and with the CoFAR grading system for allergic reactions, are provided as a general guide.

Mild Symptoms:

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

Moderate symptoms:

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

Severe symptoms:

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

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

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

In general, the severity of allergic symptoms elicited at a particular dose of study product will define the tolerability of that dose of study product. The place where there is the greatest need for clinical judgment in determining the tolerability of a dose is when the dose elicits mild allergic symptoms. Table 5 illustrates the likely combinations of symptom severity and tolerability.

Table 5: Allergy Symptom Severity and Study Product Dose Tolerability

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

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

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

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

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

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

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

Severe symptoms: If a dose elicits severe symptoms, the dose will be assessed as not tolerated. Whenever a dose elicits an allergic response characterized by 1 or more severe symptoms, the crucial decision, after adequate treatment for the allergic reaction has been administered, will be to determine whether the subject should continue in the study, dosing at a reduced dose level, or be discontinued early from the study. Please refer to individual stopping rules in Section 7.8.2.

The determination of tolerability will decide the course of action to be taken in response to dose-related reactions (Section 6.5.3).

6.5.3 Assessment of the Tolerability of a Dose Level

6.5.3.1 Assessment of Acute Symptoms Occurring After Dosing

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

The recurrence of a mild symptom or symptoms over the course of several days of home-dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated based on the criteria listed above. If the investigational site is notified of mild dose-related symptoms on 4 or more occasions during a single week during QD dosing, the subject should be brought to the CRC for dosing under direct observation for assessment of the tolerability of the dose level. If mild dose-related symptoms are noted on 7 or more occasions during a 2-week dosing interval at a given dose level on QD dosing, that dose level should be considered not tolerated and appropriate action taken (Section 6.5.5.2). Such dose level reductions for chronic/recurrent symptoms are not permitted when subjects are on QOD, BIW, QW, or QOW treatment, and consideration should be given to withdrawing such subjects from the trial and enrolling them in ARC008. If ARC008 is not available at the time this determination is made, these subjects should undergo AR101 daily dosing and visits in ARC004, until ARC008 is available.

Because of the reduced reliability inherent in the second-hand reporting of symptoms, investigators are strongly encouraged to have subjects return to the clinic to undergo dosing

under direct observation whenever acute allergic symptoms associated with dosing are reported.

6.5.3.2 Assessment of Chronic/Recurrent Symptoms

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

If symptoms arise that suggest a chronic/recurrent reaction to study product in a daily dosing regimen, the dose level should be reduced. As with acute symptoms, the level of the dose reduction should be guided by the severity of the symptoms. Symptomatic treatment is permitted (Section 6.5.5), but should be used as a supplement to dose reduction, not a substitute for it.

For chronic/recurrent GI symptoms, especially upper GI symptoms, investigators are advised to have a low threshold for instituting a dose reduction and/or for considering early discontinuation of affected subjects from the study, owing to the potential for EoE. When dose interruptions occur due to GI AEs, the subject should fill out a PEESS v 2.0 questionnaire as soon as possible (Section 7.3.3.2). Voluntary saliva collection should also ensue as per Appendix 6 for all subjects consented into this additional study. Any subject who has not consented for participation into the voluntary saliva study, and who experiences GI AEs that interrupt dosing, may be approached to provide consent and donate saliva at the time of their dosing interruption and/or withdrawal.

For Group 1 subjects determined to be having dose-limiting chronic/recurrent GI symptoms during Up-dosing, at up to and including the 20 mg/d dose level, it is advised that dosing of study product be suspended for 4 weeks and resumed at a dose level of 3 mg/day for a minimum of 4 weeks, with the first dose given in the CRC under medical supervision. If tolerated, up-dosing may resume, with caution, according to the usual schedule, as tolerated, (Note: The 4-week suspension of dosing in response to chronic/recurrent GI symptoms occurring up to and including the 20 mg/d level is the only protocol-specified exception to the rules for missed OIT delineated in Section 6.6).

For subjects who develop dose-limiting chronic/recurrent GI symptoms at the 40 mg/d dose level or above, dose reduction and re-escalation is to proceed as described in Section 6.5.5.

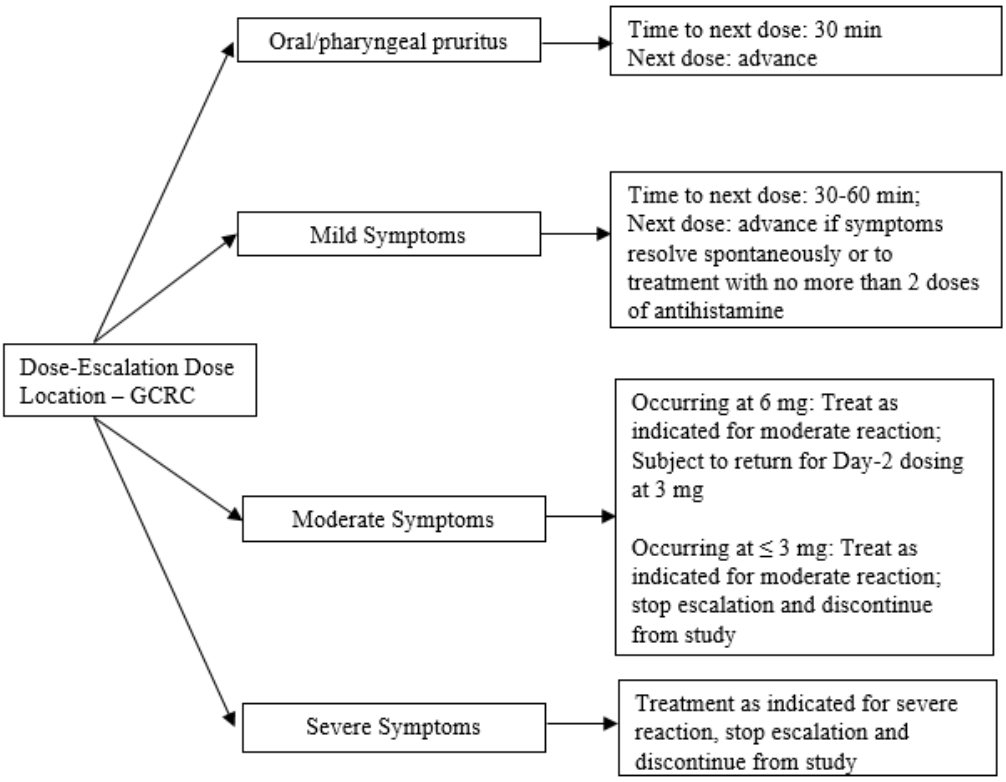
6.5.4 Treatment of Acute Reactions to Peanut OIT during Initial Escalation (Group 1)

The algorithm for managing acute allergic symptoms during OIT during the Initial Escalation, Day 1 (Group 1), is shown in Figure 2. Explanatory text follows the figure.

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

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

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



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

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

- Advance to next dose in 30 to 60 minutes, *or*
- Treat with antihistamine and then resume dose escalation within 60 minutes of last dose, provided that symptoms have resolved to the point where the investigator assesses the subject to be safe to continue dosing (ie, having no or only minimal residual signs or symptoms)
- In general, if a subject requires only 1 or 2 doses of an antihistamine to treat mild symptoms occurring during the course of the initial escalation, then the initial escalation may continue. If, however, the subject requires a second medication (eg, epinephrine or a beta-agonist) to treat the symptoms, or more than 2 doses of an antihistamine, the initial escalation is to be terminated and the subject is to receive no further OIT, even if the symptoms were assessed to be mild. Use of epinephrine to treat dose-related symptoms, even in the unlikely event that the symptoms are graded as mild, will be cause to terminate the initial escalation.

- **Moderate symptoms**: For *moderate symptoms*, if the symptoms are not worsening or amassing at a rapid pace, then a stepwise approach to treatment may be taken at the discretion of the investigator.
  - If the first action undertaken is to implement an observation period, the observation period should not exceed 30 minutes before either the symptoms are noted to be resolving or therapy is instituted.
  - Whether treatment is initiated immediately or after an observation period, the subject may be treated first with antihistamines or immediately with epinephrine, as deemed appropriate by the investigator.
  - Other therapies may be added either sequentially or simultaneously, per investigator judgment. If moderate symptoms occur at any of the doses below 6 mg (ie, up to and including 3 mg), then the desensitization procedure will be discontinued and the subject considered an escalation failure and desensitization nonresponder.
  - The decision to discontinue escalation is to be based solely on the determination of whether the allergic reaction was of moderate severity.
  - Although it is generally the case that some form of treatment will be instituted for moderate symptoms, treatment is not a requirement for assessing an allergic reaction as being of moderate severity.
- **Severe symptoms**: For *severe symptoms*, the actions taken should be to discontinue the initial escalation and administer the appropriate rescue medications. The desensitization procedure will be discontinued regardless of the dose at which the severe symptom or symptoms occurred, and the subject will be considered an escalation failure and desensitization nonresponder.

6.5.5 Treatment for Reactions During the Up-dosing Period (Group 1): Dose Adjustment

If a dose or dose level is assessed *as not tolerated*, the action taken will depend on the type and severity of the dose-related reaction and the investigator's clinical judgment. The following possible actions are at the investigator's discretion and are considered in greater detail in subsequent sections (Section 6.5.5.1, Section 6.5.5.2, Section 6.5.5.3, and Figure 2).

- Dosing the subject under medical supervision in the CRC – this is encouraged whenever there is question as to the tolerability of a dose level. It may be performed at the current dose level or at a reduced dose level, if there is already a high index of suspicion that the current dose level has not been tolerated.
- Holding dose level at current level for an additional 1 to 2 weeks before attempting dose escalation – this may be done at the discretion of the investigator if there is concern that the current dose level has not been sufficiently well tolerated to attempt up-doing to the next dose level.
- Reducing dose by 1 or 2 dose levels and maintaining the reduced dose level for 2- to 4-week period before attempting dose re-escalation – Generally, this should be the action taken when a dose that has been observed in the CRC is assessed as not tolerated, if a dose elicits moderately severe symptoms, if a single dose of epinephrine has been administered to treat a dosing reaction, or if the investigator is convinced of the intolerability of the current dose level. In short, it should be considered the default action whenever a dose or dose level is assessed *as not tolerated*.
- Reducing dose level for less than the usual 2-week period – this may be instituted as treatment for an intercurrent AE, to aid the investigator in determining if a dose level is or is not tolerated, or if a pattern of decreased study product tolerability during menses is discerned. The level of the reduction in dose, ranging from a 1-step reduction to a 50% reduction will be at the investigator's discretion, based on clinical judgment. The manner in which dose escalation may resume will depend on the level and the duration of the dose reduction.
- Temporarily withholding study product dosing – this may be instituted as treatment for an intercurrent AE or to aid the investigator in determining if a dose level is or is not tolerated, but the duration of withholding study product may not exceed 14 consecutive days, or the subject will be discontinued from the study. The manner in which dosing may resume after withholding dosing of study product depends on the duration for which dosing was withheld.
- Reducing dose by 2 dose levels and maintaining the reduced dose level for ≥ 6 weeks – continuing dosing at a reduced dose level for ≥ 6 weeks prior to attempting re-escalation is mandatory if 2 doses of epinephrine are given to treat a single AE.
- Stopping dosing and discontinuing the subject early from the study – this is an option that the subject may elect at any time and for any reason. The investigator must discontinue the subject from further dosing and continuation in the trial under circumstances that could jeopardize the health of the subject or the integrity of the trial.

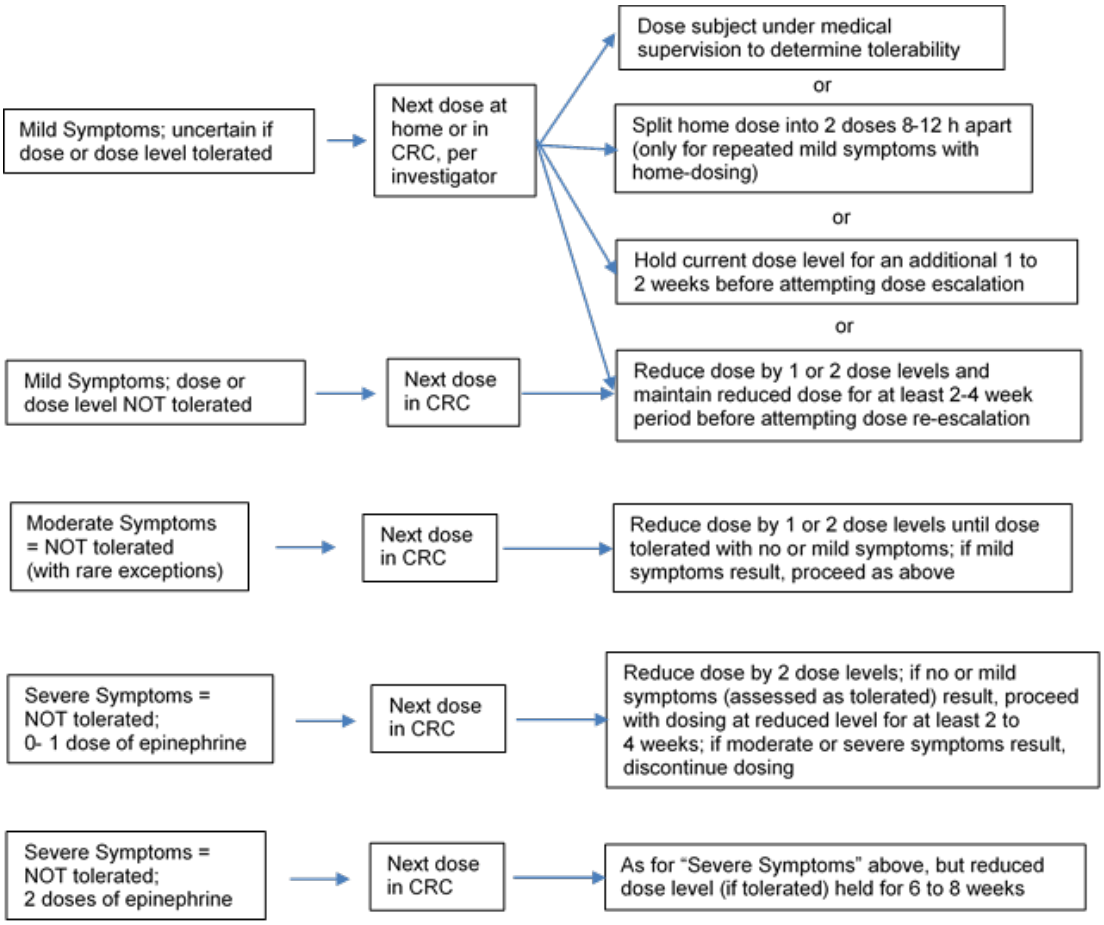
6.5.5.1 Reactions to In-Clinic Dosing (Group 1)

6.5.5.1.1 Up-dosing Tolerated at First Dose at New Dose Level

The scenarios listed below describe a subject considered to have tolerated the first dose at a new dose level. The procedures outlined for each scenario should be followed.

- No symptoms: If a subject undergoes up-dosing in the CRC without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the CRC for the next scheduled dose escalation visit 2 weeks later.
- Oral/pharyngeal pruritus only: If the subject experiences *oral/pharyngeal pruritus* only following the administration of the first dose at a new dose level, the dose will generally be *assessed as tolerated*, and the same dose can be repeated the next day at home and continued throughout the 2-week home-dosing interval, unless other symptoms indicative of lack of tolerability begin to develop.
- Mild symptoms, tolerated at first dose at new dose level (see Section 6.5.1 for definitions of *mild symptoms*): If *mild symptoms* occur with the first dose at a new dose level and the dose is *assessed as tolerated*, the action taken should be to repeat the same dose the next day. It is advised that the repeat (next day's) dose be administered in the CRC, but it may be given at home, at the investigating physician's discretion. If the second dose at the new (increased) dose level is tolerated without symptoms, then the subject is to continue that dose level for the requisite 2 weeks and return to the CRC for up-dosing at the next scheduled visit. If the dose again causes mild symptoms, but is *assessed as tolerated*, the subject may continue at that dose level or return to the last tolerated dose (at the investigator's discretion) and continue dosing at home for the next 2 weeks at the investigator-determined dose level. (See Section 6.5.5.2 for actions to be taken in the event that symptoms develop during home-dosing.) If, following the first dose at a new dose level, the second dose at the new (increased) dose level is again accompanied by mild symptoms, but is *assessed as not tolerated*, the procedures outlined in the paragraph above should be followed. The algorithm for management of dose adjustments due to poorly tolerated doses is depicted in Figure 3. Explanatory text follows the figure.

Figure 3: Schematic for Management of Dose Adjustments due to Poorly Tolerated Doses (Groups 1 and 2)



- Mild symptoms that indicate uncertainty regarding tolerability: If *mild symptoms (*see Section 6.5.1 for definitions of *mild symptoms*), other than *oral/pharyngeal pruritus* occur with the first dose at a new dose level and there is uncertainty about whether the dose is tolerated, the investigator will determine whether the subject should receive the next dose in the CRC or at home. If the investigator determines that the subject requires medical supervision to determine tolerability, the subject should receive the next dose at the CRC. If the investigator determines that the subject does not need medical supervision, the procedure will be to split the home dose into 2 doses taken 8 to 12 hours apart.
- Mild symptoms that indicate lack of tolerability: If *mild symptoms* other than *oral/pharyngeal pruritus* occur with the first dose at a new dose level and the dose is *assessed as not tolerated*, the action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose (ie, a 1-step dose reduction) under medical supervision (if the subject is unable to return to the CRC on the day specified, the investigator may initiate an approximate 1 dose-level reduction at home, with the subject coming to the CRC at the earliest date possible).

If the reduced dose is *assessed as tolerated*, the subject is to continue that daily home dose for the ensuing 2 weeks. (See Section 6.5.5.2 for actions to be taken in the event that symptoms develop during home-dosing.) If the reduced dose is again *assessed as not tolerated*, the subject is to return to the CRC the next day for supervised dosing at a 1- or 2-step reduction in dose (per investigator judgment, based on severity of reaction). If this further reduced dose is *assessed as tolerated*, the subject will continue at that dose level for daily home-dosing over the ensuing 2 weeks. If, however, the reduced dose is *assessed as not tolerated*, the subject is to be considered an escalation failure non-responder.

- Moderate symptoms occurring with a new dose level would indicate lack of tolerability, with rare exceptions. Exceptions would generally be for a transient, self-limited (requiring no intervention and resolving completely) symptom of moderate intensity occurring in a single organ system. In addition, the symptom would typically be subjective. Any dose associated with moderate symptoms and assessed as tolerated must be accompanied by a brief explanation in the CRF as to why the dose was considered tolerated; (see Section 6.5.2, for moderate symptoms assessed as tolerated). If moderate symptoms occur with the first dose at a new dose level, except for rare instances described above, the dose will be *assessed as not tolerated*. The action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose under medical supervision. If this reduced dose elicits no allergic symptoms (ie, is well tolerated), the subject will continue that daily home dose level for an additional 2 weeks.

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

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

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

Severe symptoms requiring 0 to 1 dose of epinephrine: If a subject experiences severe symptoms requiring 0 to 1 dose of epinephrine, the procedure is to have the subject return to the CRC for the next dose and to reduce the dose by 2 dose levels. If no or mild symptoms (assessed as tolerable) occur, dosing may proceed at the reduced level for at least 2 and up to 4 weeks. If moderate or severe symptoms occur, dosing is to be discontinued.

Severe symptoms requiring 2 doses of epinephrine: If a subject experiences severe symptoms requiring 2 doses of epinephrine, the procedures outlined in the above paragraph should be followed; however, dosing will proceed at the reduced dose level (if tolerated) for at least 6 and up to 8 weeks.

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

6.5.5.1.2 Up-dosing: Tolerability Uncertain or No Tolerability at First Dose at New Dose Level

If a subject has symptoms in the CRC after up-dosing that suggest the dose was not tolerated, or suggest that tolerability of the dose is uncertain, the investigator must assess the tolerability, as outlined in Section 6.5.3. The algorithm for management of dose adjustments due to poorly tolerated doses is depicted in Figure 3. Explanatory text follows the figure.

6.5.5.2 Reactions to Dosing at Home (Groups 1 and 2)

With the occurrence of symptoms of an acute reaction to study product after home-dosing, or any acute allergic reaction, subjects/parents or guardians are instructed to call the study site. The investigator must then determine whether or not the dose was tolerated (Section 6.5.3). Because of the reduced reliability inherent in the second-hand reporting of symptoms, investigators are strongly encouraged to have subjects return to the clinic to undergo dosing under direct observation whenever acute allergic symptoms associated with dosing are reported.

When symptoms of a dose-related allergic reaction are reported during the course of daily home-dosing, the investigator must assess the severity of the reaction and whether the dose associated with the reaction was tolerated. The appropriate intervention will depend on the type and severity of symptoms (Section 6.5.5).

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

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

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

- Continue with daily home dosing at the current dose level.
- Continue the same daily dose for the rest of the 2-week interval, with the dose split into 2 fractional doses given 8 to 12 hours apart (the 2 fractional doses need not be equal).
- Return to the CRC for repeat dosing at the current dose level under direct observation to confirm whether or not the dose level is tolerated.
- Return to the CRC for dosing of a previously tolerated dose level, either a 1- or 2-step reduction (per investigator judgment, based on severity of reaction) and follow the procedures described in Section 6.5.5.2 above.
- Institute the 4-week hiatus from dosing, with resumption of dosing at the 3 mg/d dose level, as permitted for recurrent GI symptoms occurring at or before the 20-mg dose, as described in Section 6.5.3.2.
- Discontinuation of dosing.

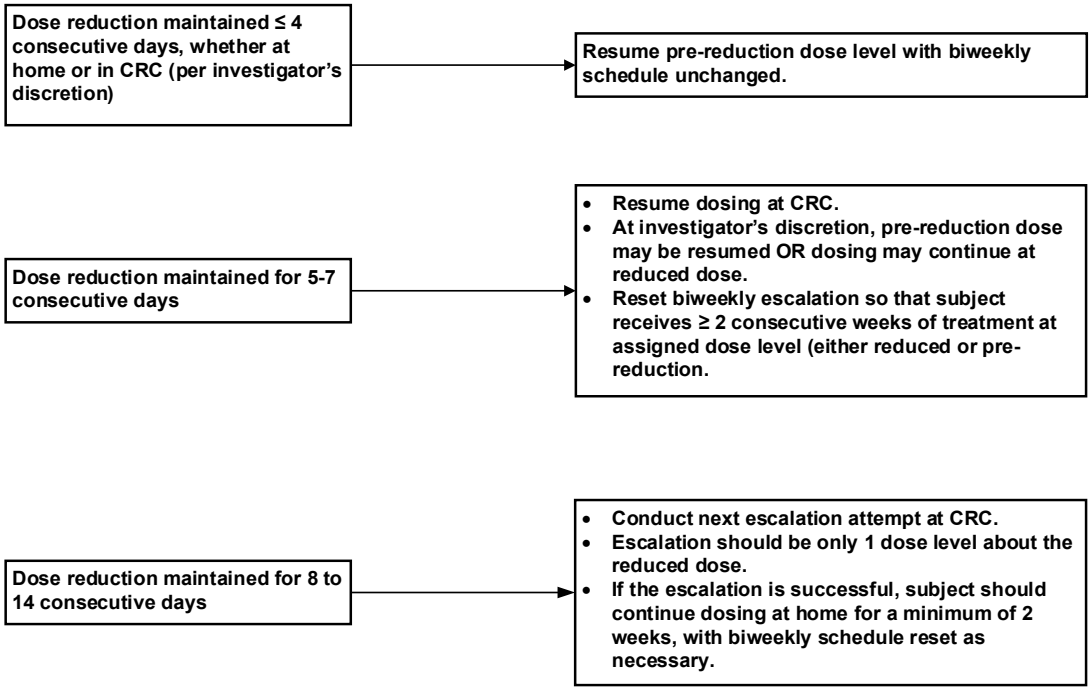
Any subject who discontinues up-dosing due to severe or repeated allergic reactions to study product should have his/her mechanistic blood draw and CBC (Section 6.4) at, or as soon as possible to, the time of the last dose and no later than at his or her Early Discontinuation Visit.

Home dosing symptoms during nondaily EM regimens are handled separately and discussed further in Section 6.5.7.

6.5.5.3 Dose Adjustment in Response to Intercurrent Adverse Events (QD Regimens only)

At the investigating physician's discretion, temporary dose reductions, ranging from a 1-step reduction (ie, to the previous dose) to approximately half of the current dose level (to the nearest feasible available whole dose), can be instituted as part of the treatment regimen for an intercurrent AE. Also, if a pattern of decreased tolerability of study product during menses is discerned, then a temporary dose reduction can be instituted during this time. A schematic showing procedures for temporary dose reductions due to intercurrent AEs is provided in Figure 4; explanatory text follows the figure.

Figure 4: Schematic for Temporary Dose Reductions due to Intercurrent Adverse Events (QD Regimens Only)



CRC = clinical research unit; QD = daily.

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

Doses of study product may also be withheld at the investigator's discretion, in response to an intercurrent AE. Doses withheld as part of the treatment for an AE constitute a special category of missed peanut OIT doses (Section 6.6).

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

The treatment(s) for types of reactions during the Up-dosing period are summarized by severity of reaction in Table 6.

Table 6: Treatment(s) for Reactions during the Up-dosing Period by Severity of Reaction

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

Assessment of severity of reaction is described in Section 6.5.1. Assessment of tolerability of an individual dose is described in Section 6.5.2.

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

  Many mild acute allergic reactions can be transient and self-limiting, requiring no therapeutic intervention. Others, however, may require treatment. Generally, for mild symptoms requiring treatment, the subject should receive antihistamines.
- Acute allergic reactions manifesting with moderate symptoms will generally require therapeutic intervention, although some, even moderate, symptoms may on rare occasion be so transient as to require no specific treatment. Generally, for moderate symptoms requiring treatment, the subjects should receive antihistamines and/or epinephrine, as indicated. If there is uncertainty as to the severity of the reaction, administering epinephrine would be considered the most appropriate course of action.
- Generally, severe symptoms will require treatment with epinephrine at a minimum. If severe symptoms that qualify as stage 3 anaphylaxis (as defined in Appendix 3) occur at any time, dosing with study product will stop and the subject will be discontinued from the study as an escalation failure nonresponder.

The procedures(s) that should be implemented after treatment of a reaction experienced during the Up-dosing period are summarized in Table 7. An explanation follows the table.

Table 7: Procedure(s) Following Treatment of a Reaction Experienced during the Up-dosing Period

Treatment Given for Reaction	Procedure(s) Following Treatment
Antihistamines only	• Continue dose escalation
Epinephrine: ≥2 doses taken either in CRC or at home	• Discontinue dosing • Subject returns to CRC 14 days after last dose for Early Discontinuation Visit
Epinephrine: single dose given in CRC	• Stop dosing at CRC • Reduce next dose by 2 doses, both to be administered at CRC • Continue bi-weekly escalation
Epinephrine required for a second consecutive time during, or after, 1 escalation attempt	• Dose reduced by 2 dose levels. • Reduced dose level continued for 6 to 8 weeks • Escalation may be attempted after 6 to 8 weeks
Epinephrine required for a third consecutive time during an escalation attempt	• Discontinue dosing • Subject returns to CRC 14 days after last dose for Early Discontinuation Visit
Epinephrine: single dose at home	• Not counted in the total count of epinephrine uses unless severe anaphylaxis has occurred • Subject returns to CRC for an observed dose under medical supervision prior to resuming any dosing at home

CRC = clinical research center.

- Antihistamines

  If a subject receives antihistamines only, the dose escalation can be continued. If epinephrine is administered, then a different course of action is to be taken (see below).

- Epinephrine – General Procedures

  Any reaction to study product (in clinic or at home) that requires more than 2 doses of epinephrine will halt all further dosing of study product for the individual. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10).

- Epinephrine – Single Dose Administered at Clinic

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

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

If a *single administration of epinephrine is required for a third consecutive time* during an escalation attempt, no further dosing should be attempted. Dosing in these subjects will be discontinued. They will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10).

- Epinephrine – Home

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

6.5.7 Reactions Occurring During the Maintenance and Extended Maintenance Periods (Groups 1 and 2)

Dosing guidelines following treatments given for reactions experienced by subjects in Groups 1 and 2 receiving AR101 at 300 mg QD, QOD, BIW, QW, or QOW during the Maintenance and Extended Maintenance period are summarized in Table 8. A textual explanation follows the table.

Table 8: Dosing Guidelines Following Treatment for Reactions Experienced by Subjects in Groups 1 and 2 Receiving AR101 at 300 mg QD, QOD, BIW, QW, or QOW During Maintenance and Extended Maintenance

Treatment Regimen	Dosing Guidelines and Procedures
QD	Follow Up-dosing procedures.
QOD, BIW, QW, or QOW	• Withhold the scheduled dose until the AE is resolved and the dose can be safely administered. • Reset the interval between doses after the subsequent dose is tolerated. – If the dose must be withheld for > 3 days past when the dose was due to be taken, the investigator must discuss the case with the Sponsor's Medical Monitor prior to administering the next dose. Dosing options are described in the text following this table.

BIW = twice weekly; QD = once daily; QOW = every other week; QW = once weekly.

- This phase consists of the subject receiving the 300-mg dose of study product either QD, QOD, BIW, QW, or QOW. For any symptoms noted during the QD Maintenance or EM period, the same study product dosing guidelines and procedures

for QD dosing will be followed as for the Up-dosing Period. However, for subjects on nondaily regimens, the following guidelines and procedures apply:

- The tolerability of doses on nondaily dosing regimens will be evaluated as in Section 6.5.2, keeping in mind the individual stopping rules related to tolerability and symptom severity as outlined in Section 7.8.2.
- In the event of a clinically significant intercurrent AE occurring at the time of a scheduled QOD, BIW, QW, or QOW dose, subjects should be advised to withhold the scheduled dose until the AE is resolved and the dose can be safely administered; the interval between doses should be reset once the subsequent dose is tolerated.
- *If the dose must be withheld for > 3 days past when the dose was due to be taken*, the investigator must discuss the case with the Sponsor's Medical Monitor prior to administering the next dose. Options available at that time include, but are not limited to, any of the following:
  1. Continue ARC004 and administer the next 300 mg dose under supervision at the CRC.
     - If tolerated, continue EM dosing at 300 mg on the same schedule, resetting the dosing interval;
     - If not tolerated, consider options 2 or 3 below.
  2. Continue ARC004 and administer approximately half of the 300 mg dose under supervision at the CRC. The entire 300 mg dose should be prepared with the preferred vehicle and then approximately half of the dose should be administered; *the remainder should be discarded*. If not tolerated, the subject should be discontinued from the study. If tolerated, up to 3 successive doses can be administered this way according to the subject's assigned schedule, but then 300 mg should again be attempted.
  3. Discontinue the subject from ARC004 and consider enrollment in ARC008 if the site has received approval to enroll subjects in ARC008. This should be the preferred option for any subject on a QOD, BIW, or QW dosing regimen whose interval between AR101 doses exceeds 14 days. If the subject is at a site that has not yet received approval to enroll subjects in ARC008, the subject may start AR101 daily dosing and have visits in the Repeat Up-dosing Period in ARC004 until ARC008 is available.

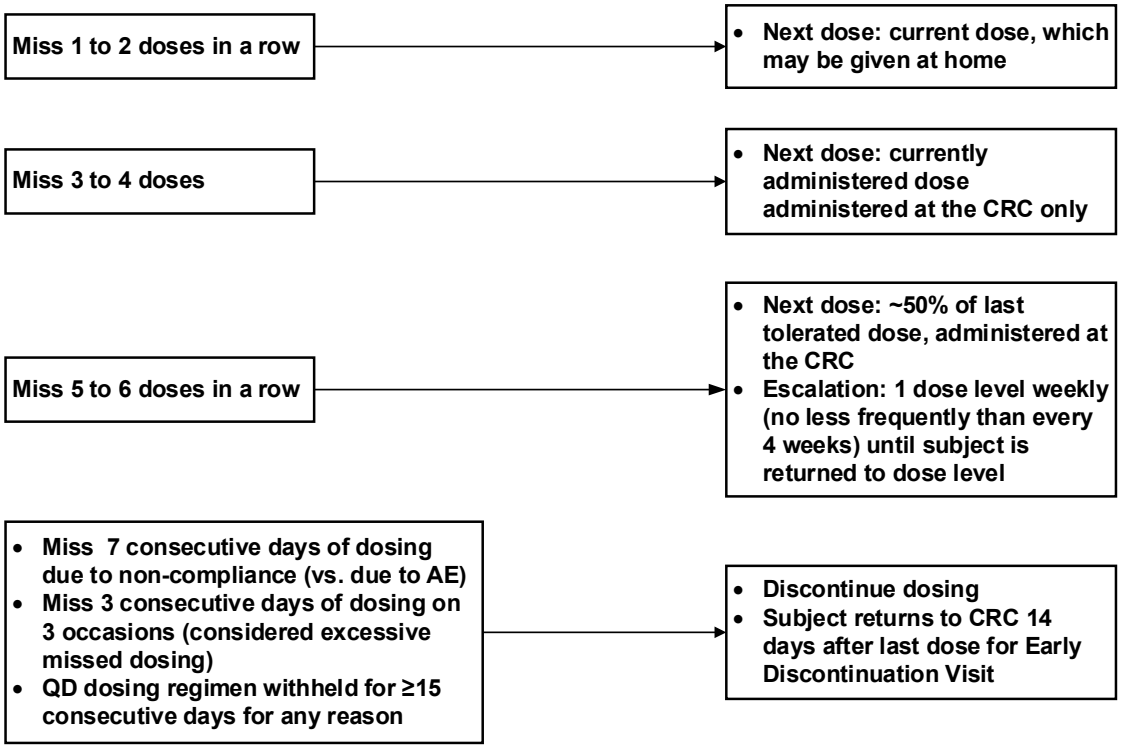
- For subjects having acute reactions to QOD, BIW, QW, or QOW doses, appropriate treatment and follow-up is to be administered per Section 6.5.6. As mentioned in Section 7.8.2, any EM subject on QOD, BIW, QW, or QOW dosing having 1 related SAE; 1 related AE graded severe; 2 related AEs occurring on separate occasions, both graded moderate; or 3 consecutive doses judged "not tolerated," will be considered as a treatment failure and discontinued from ARC004 for safety reasons. Such subjects may be eligible to enroll in ARC008 and return to a QD regimen. If a site has not yet received approval for enrollment of subjects in ARC008, the subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.

- Sites will ensure that all subjects have in-date epinephrine autoinjectors, appropriate anaphylaxis teaching, and access to emergency services as per local standards.

6.6 Missed Peanut OIT (Study Product) Doses during Up-dosing (Group 1)

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

Figure 5: Procedures Following Missed Consecutive Doses of Peanut OIT



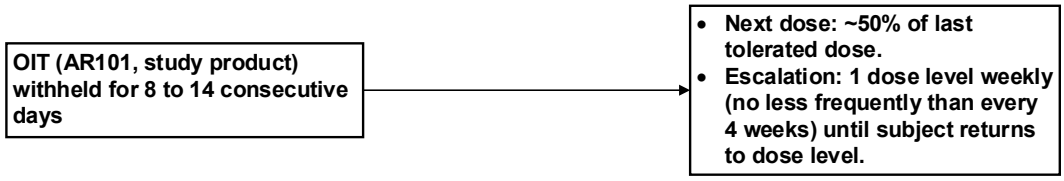
AE = adverse event; CRC = clinical research unit; OI = oral immunotherapy (ie, AR101 or study treatment).

- Miss 1-2 doses in a row – The next dose would be the current dose level and could be given at home
- Miss 3-4 doses in a row – The next dose would be the current dose and would be given under supervision in the CRC
- Miss 5-6 doses in a row – Initiate the next dose at approximately 50% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 50% of the last tolerated dose). This dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1 dose level occurring no more frequently than weekly and generally no less frequently than every 4 weeks

until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the up-dosing period apply.

- Missing ≥ 7 consecutive days of dosing due to non-compliance (ie, for any reason other than treatment of an AE or a study product dispensing error), constitutes an individual stopping rule and the subject is to stop taking study product. The subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10).
- Additionally, excessive missed dosing, defined as 3 consecutive days of missed doses on 3 occasions during the Up-dosing Period, for any reason other than treatment of an AE, constitutes an individual stopping rule and the subject is to stop taking study product. The subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10).
- If study product has been withheld for 8 to 14 consecutive days as treatment for an AE or due to a study product dispensing error, dosing may be reinitiated at approximately 25% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 25% of the last tolerated dose) if the lapse in dosing occurred during the *Up-dosing Period*. If the lapse in dosing occurred during the *Maintenance Period*, (see Figure 6) 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.

Figure 6: Procedures for Doses Withheld for 8 to 14 Days During the Maintenance Period



OIT = oral immunotherapy (ie, AR101, study product).

- If a subject on a QD dosing regimen has his/her study product withheld for ≥ 15 consecutive days for any reason, at any point in the study (with the exception of a dosing hiatus instituted for chronic/recurrent GI AEs at or before the 20 mg dose level, as per Section 6.5.3.2), the subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (Section 6.3.10).

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

6.7 Skin Prick Test

Subjects will have SPTs performed using 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.

6.8 Visit Windows

Strict adherence to the dosing schedule should be maintained:

- Study visits should occur within a ± 2-day window of the scheduled visit date (ie, 2 days before or 2 days after the scheduled visit date) for all phases of the study until Week 14 of the EM phase.
- Starting at Week 14 of the EM phase, the permissible window around study visits will be extended to 1 week before or 1 week after a planned in-clinic dosing visit (ie, ± 1 week).
- The Early Discontinuation Visit is to occur 14 days after the last dose of AR101. The permissible window is minus 3 days to plus 7 days for those subjects who will permanently discontinue AR101 treatment.
- Study visits for scheduled blood draws or DBPCFC should take place within 2 weeks of the scheduled visit.

6.9 Other Safety Assessments

6.9.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in the Schedules of Events (Appendix 1). Height and weight will also be recorded. Vital signs will also be assessed, including BP, PR, and body temperature.

6.9.2 Prior and Concomitant Medications

Prior and concomitant medications will be documented in the CRF.

6.9.3 Pregnancy Test

All female subjects of child-bearing potential will undergo serum pregnancy testing at baseline and then routine urine pregnancy testing throughout the study at the visits indicated per protocol (Section 6.3).

7 SAFETY MONITORING

This section defines the types of safety events that should be reported and outlines the procedures for appropriately collecting, grading, recording, and reporting them. A Safety Monitoring Committee (SMC) will be established to monitor study safety events and will meet approximately quarterly throughout the study.

7.1 Definitions

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

- Any allergic symptoms observed during in-clinic dosing will be recorded directly on the Escalation/In-Clinic Dosing Form (also referred to as a Study Product Administration Form), and are not recorded on an AE form (to avoid duplicate reporting) unless the event is considered an SAE. These symptoms are, however, by definition, AEs (Section 7.2) and will be reported as such in the database.
- Non-serious AEIs are reported on an AEI form and include anaphylaxis episodes meeting the criteria below, accidental food allergen exposures, GI AEs resulting in prolonged disruption of dosing, AEs associated with the use of epinephrine, and severe AEs (Section 7.3.3). They are not to be reported on an AE form (to avoid duplicate reporting) unless the event is considered an SAE, as defined below (Section 7.3.2).
- If any safety event meets the definition of an SAE (whether or not related to dosing), it will also be recorded on an AE/SAE form.
- Skin prick test reactions are not considered AEs unless the reaction, or a complication from the procedure, is considered an SAE, as defined below (Section 7.3.2).
- Food challenge reactions that occur in the clinic are captured on study specific forms and are not reported on an AE form (to avoid duplicate reporting) unless the event is considered an SAE, as defined below (Section 7.3.2).
  - As study product is not used in the DBPCFCs, no AEs occurring from Screening DBPCFC can be treatment-related (referring to treatment with study product).
  - For food challenge reactions that occur at the Exit DBPCFC, it will also usually be the case that study product was not the cause of the reaction, as study product is not used in the challenge. There is, however, the possibility that dosing with study product in the days prior to Exit DBPCFC could contribute to a reaction encountered during the challenge. The investigator must determine if dosing with study product in the days prior to Exit DBPCFC likely contributed to any observed reaction. If so, the investigator should indicate the level of the relatedness, and provide a brief explanation as to the manner in which prior dosing with study product was thought to be contributory.
- All SAEs are reported on the AE/SAE form set in addition to the Skin Prick Test form or an Oral Food Challenge form if the event occurred during 1 of these

procedures. All other safety events that occur throughout the study are reported on the AE/AEI/SAE form set.

7.2 Dosing Symptoms as Adverse Events

Although signs and symptoms of allergic reaction, especially those that are mild in severity, are frequent and expected occurrences in response to dose escalation during OIT, they still constitute AEs. As such, the start and stop times of dose-related allergic reactions, as well as any therapeutic interventions, and relatedness to study product will need to be recorded (Section 7.5.1).

It is common for allergic reactions, especially allergic reactions to food allergens, to manifest with multiple symptoms. When multiple symptoms are noted during the same episode, it is up to the investigator to determine whether 1, or more than 1, AE has occurred. For allergic/ hypersensitivity reactions involving multiple symptoms, each individual symptom is to be entered on a separate log line on the AE electronic CRF (eCRF). For each symptom, the AE eCRF will query "Is this an allergic reaction?" and the site should indicate yes/no accordingly.

7.3 Definitions of Safety Events

7.3.1 Adverse Event (AE) or Medical Event

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

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

An adverse reaction is any AE caused by the drug.

7.3.2 Serious Adverse Events (SAE)

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

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

6. Important medical event that may not result in 1 of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent 1 of the outcomes listed in the above definition of serious event.

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

7.3.3 Adverse Events of Interest

7.3.3.1 Anaphylaxis Events

An anaphylaxis event is an AE that meets the definition of anaphylaxis in the 2014 position paper by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines Group (Muraro et al, 2014). Accordingly, anaphylaxis is defined as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems that is usually, though not always, associated with skin and mucosal changes.

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

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

For the purposes of this protocol, symptoms during DBPCFCs are not considered to be anaphylaxis events.

7.3.3.2 Gastrointestinal Adverse Events Resulting in Prolonged Disruption of Dosing

Gastrointestinal AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered AEIs and will be assessed longitudinally according to the procedures described below. For the purpose of delineating these AEIs, prolonged

disruption of dosing is defined as withholding study product for > 7 days. This will include 3 categories of subjects:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2);
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2);
- Any subject who permanently discontinues dosing who had experienced a GI AE (Section 7.3.3.2).

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

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

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

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

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

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

7.3.3.3 Accidental Food Allergen Exposures

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

To report the occurrence of a safety event associated with accidental food ingestion, subjects will be instructed to contact the site study coordinator or investigator after any known or suspected food allergen exposure, even if it does not cause symptoms. The subject may be asked to return to the site. These events will be reported as follows:

- The non-serious AEI form will be completed for each of these events, in addition to events where consumption of peanut without a reaction occurs, *unless*:
- The accidental food ingestion safety event meets the definition of an SAE, as defined below (Section 7.3.2), in which case the SAE form will be completed.

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

7.3.3.4 Adverse Events Featuring a Severe Symptom

The severity of symptoms will be determined based on the investigator's judgment. Severity definitions for allergic reactions to investigational product were developed to be consistent both with the PRACTALL consensus report and with the CoFAR grading system and are provided in Section 6.5.1 and the table in Appendix 4 as a general guide. Severe allergic AEs may include:

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

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

If the severe AE was part of an allergic reaction that meets criteria for anaphylaxis, an accidental food allergen exposure, an AE featuring a severe symptom, or an SAE, it need not be reported separately. The intent of this AEI is to capture events that may be occurring that do not fall into one of these other categories.

7.3.3.5 Adverse Events Associated with Use of Epinephrine

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

whether it was administered in the CRC or at home. If the epinephrine was used as part of an allergic reaction that meets criteria for anaphylaxis, an accidental food allergen exposure, an AE featuring a severe symptom, or an SAE, the use need not be reported separately. The intent of this AEI is to capture events that may be occurring that do not fall into 1 of these other categories.

7.4 Severity Grading

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

- The severity grading of allergic reactions will be according to the definitions developed by the CoFAR group (Appendix 4)
- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 3).
- For grading the severity of all other AEs, the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) system will be used. The purpose of using the NCI-CTCAE system is to provide standard language to describe AEs ("toxicities") and to facilitate tabulation and analysis of the data and for assessment of the clinical significance of treatment-related toxicities. The NCI-CTCAE provides a term and a grade that closely describes the AE. Each participating site will receive copies of the grading scales and event descriptions.

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

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

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

7.4.1 Guidelines for Determining Causality of an Adverse Event

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

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

7.5 Adverse Event Collection Procedures

Any new event or experience that was not present at Screening, or worsening of an event present at Screening, is considered to be an AE. Unchanged, chronic conditions are not AEs and should not be recorded on the AE page of the CRF. Adverse events will be evaluated from the onset of the event until the time the event is resolved or medically stable, or until 30 days after the Exit or Early Discontinuation Visit, whichever comes first. Adverse events ongoing at the time that study treatment is discontinued may not be determined to be medically stable until 30 days after the Exit or Early Discontinuation Visit has been conducted, in which case additional visits after the Exit or Early Discontinuation Visit may be required. For the specific case of GI-related AEIs, the need for additional follow-up is outlined in Section 7.3.3.2. Investigators should also report AEs discovered after cessation of dosing and prior to the Early Discontinuation Visit.

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 symptom logs (provided to record symptoms between visits)

7.5.1 Recording and Reporting Procedures

A multi-screen AE eCRF will be used allowing all AEs to be submitted through a single reporting mechanism (Figure 7). Serious AEs will require additional information reported on additional screens within the EDC system. Source documents, with subject identifiers redacted, can be scanned and attached to the AE form as well. The investigator will treat subjects experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

7.5.2 Serious Adverse Event Recording and Reporting Procedures

Serious AEs will be recorded on the AE CRF. All centers are obligated to report SAEs within 24 hours of their occurrence and/or the site's knowledge of the event to the Sponsor. The following attributes will be assigned:

- Description
- Date of onset and resolution (if known when reported)

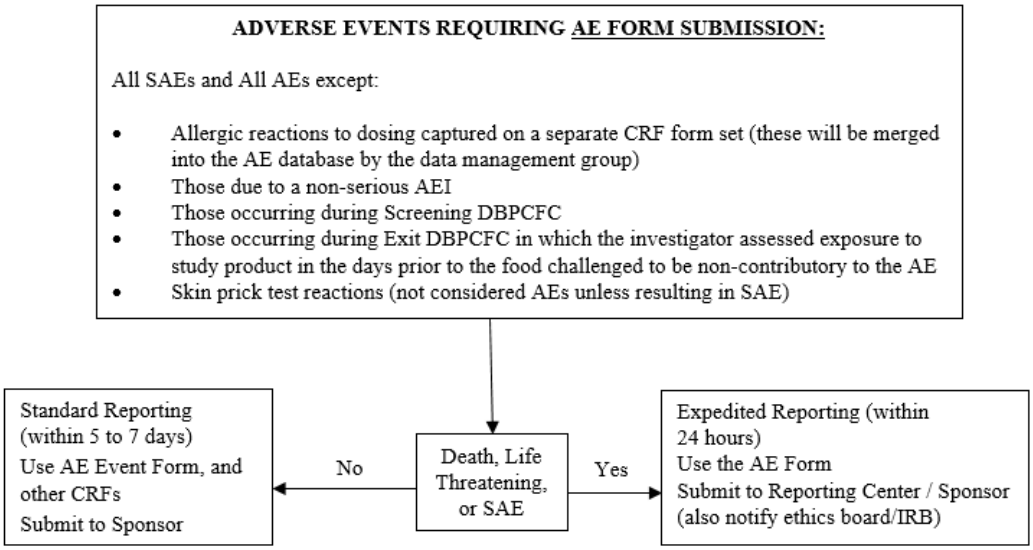
- Severity
- Assessment of relatedness to test article
- Action taken

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

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

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

Figure 7: Reporting Decisions for Adverse Events



Steps to follow in sequence:

1. Site to notify the site's Principal Investigator of event(s).
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 (death certificate, medical notes, etc.).

7.6 Serious Adverse Event Notification

7.6.1 Notifying the Sponsor

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

7.6.2 Expedited SAEs Reporting to Regulatory Health Authorities

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

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

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

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

7.6.3 Other Events Reportable to the Sponsor

Investigational sites are instructed to report all episodes of anaphylaxis meeting the criteria in Appendix 3 within 24 hours of their awareness of the event to the Reporting Center; others can be reported within 7 days. An initial Anaphylaxis Episode form containing the information known to the site at this time will be transmitted to the Reporting Center. The Reporting Center will then relay to the Sponsor the individual anaphylaxis reports as they are obtained. The investigational site will supplement the initial Anaphylaxis Episode report with

additional information pertaining to an event as it becomes available and will forward the information to the Reporting Center. The Sponsor's Medical Monitor reviews these events upon receipt and will expedite anaphylaxis events to the SMC 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 events meeting seriousness criteria will be reported as per other SAEs, as outlined above in Section 7.5.2, but in general will not be further reported in expedited fashion to regulatory health authorities unless meeting the criteria of a SUSAR.

7.6.4 Review Board and Ethics Committee

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

7.7 Other Safety Assessments and Precautions

7.7.1 Physical Examination and Vital Signs

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

7.7.2 Prior and Concomitant Medications

Prior and concomitant medications will be documented in the CRF.

7.7.3 Pregnancy Testing and Contraception

7.7.3.1 Pregnancy Testing

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

7.7.3.2 Contraception

Subjects undergoing OIT are at increased risk for experiencing allergic reactions and may be at increased risk for experiencing anaphylaxis. Anaphylaxis can cause a dangerous drop in

blood pressure; if this were to occur during pregnancy, it could result in compromised placental perfusion and significant risk to the fetus.

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

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

A postmenopausal state is defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy. A single FSH measurement is considered sufficient only in a female who had amenorrhea for at least 12 months.

Investigators must ensure that all female subjects who are post-menarchal are provided with age-appropriate counselling and information about contraception, including adequate information about the use, effectiveness and side-effects of contraceptive methods.

Female subjects are to use either:

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

7.8 Stopping Rules

7.8.1 Overall Stopping Rules

Considerations for early termination of a subject are listed in Section 4.3.1. In addition, this protocol will institute the following stopping rules. The study will be suspended at any time that a treatment-associated death occurs in a subject receiving AR101 active therapy, or that the second of 2 subjects is admitted to the hospital, within 6 months of the first, as a direct consequence of dosing with AR101. Suspension of the study will entail halting the enrollment of subjects and refraining from any dose increases, but will not entail cessation of dosing unless so directed by the relevant competent authority and agreed to by the Sponsor.

The suspension will not be lifted and dose escalation will not be resumed until the information has been discussed with regulatory authorities and the regulatory authorities either concur with resumption of up-dosing or direct discontinuation of the study in their jurisdictions.

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

7.8.2 Individual Stopping Rules

Individuals may stop the study at any time by withdrawing their consent if they experience subjectively intolerable AEs, dosing symptoms, or for any other reason. Because ARC004 is exploring alternative dosing schedules, the approach to individual stopping rules caused by dose-related AEs varies by regimen. All subjects discontinuing the study early and permanently discontinuing AR101 treatment will return to the CRC for an Early Discontinuation Visit no later than 14 days after the last AR101 exposure.

QD Dosing Regimens

When on QD dosing regimens (including Up-dosing and Maintenance for Group 1, and QD EM for both Groups, as applicable), 7 or more consecutive days of missed daily dosing due to non-compliance constitutes an individual stopping rule. During Up-dosing, Group 1 subjects must halt up-dosing and re-start with a reduced dose if more than 4 days of dosing are missed. Missing 3 or more consecutive days on 3 occasions while on daily dosing in any period is an individual stopping rule, as is missing 15 or more consecutive days of QD dosing for any reason.

QOD, BIW, QW, or QOW Regimens

Any subject receiving nondaily dosing (QOD, BIW, QW, or QOW) who has 1 related SAE; 1 related AE graded severe; 2 related AEs occurring on separate occasions, both graded moderate; or 3 consecutive doses judged “not tolerated” will be considered as a treatment failure and discontinued from ARC004 for safety reasons. Such subjects may be eligible to enroll in ARC008 and receive AR101 daily in the Repeat Up-dosing period. If ARC008 is not available, the subjects will begin daily dosing and have visits in the Repeat Up-dosing period in ARC004. Once the subject reaches the target dose of 300 mg daily and maintains that dose for 2 weeks, that subject will be able to continue this dose regimen until ARC008 is available.

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

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

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

7.8.3 Cohort Stopping Rules

ARC004 will consecutively enroll eligible subjects into different cohorts, each of which will produce evidence during the trial concerning the feasibility and safety of adjusting EM dosing from daily to a less frequent schedule. The information that becomes available as each cohort proceeds through the study will be evaluated before determining whether the next cohort is to advance to a longer interval between doses. No subject will be exposed to a regimen with longer dosing intervals (eg, QOD to BIW, BIW to QW, or QW to QOW) if evidence from the previous cohorts suggests that doing so would more likely than not cause subjects at the new interval to either experience more frequent or more severe AEs, or lose desensitization that they may have gained/maintained, had they remained on more frequent dosing. Because they will have had 28 additional weeks of QD maintenance, Cohorts 3B and 3C will be allowed to proceed to QOD and BIW dosing independent of Cohort 2's experience according to the judgment of the Safety Monitoring Committee (SMC).

For each cohort, all subjects discontinuing early due to AEs (eg, dropouts) will be considered failures. Likewise, subjects who lose protection during their ARC004 Exit DBPCFC, when compared either to their ARC003 Exit DBPCFC (Group 2), or their ARC004 Post-Maintenance DBPCFC (Group 1) will be considered failures (eg, failed completers), as follows:

- Subjects tolerating 443 mg at the previous DBPCFC must tolerate ≥ 443 mg at the ARC004 Exit DBPCFC, or be considered a failure
- Subjects tolerating 1043 mg at the previous DBPCFC must tolerate ≥ 443 mg at the ARC004 Exit DBPCFC, or be considered a failure
- Subjects tolerating 2043 mg (or greater, for Group 1 subjects) at the previous DBPCFC must tolerate ≥ 1043 mg at the ARC004 Exit DBPCFC, or be considered a treatment failure

The treatment failure rate in each cohort will be monitored on an ongoing basis by the SMC, and calculated according to the following formula:

Treatment failure rate = [(dropouts) + (failed completers)] / planned size* for the cohort

Whenever this number is greater than 50%, then this stopping rule is met and further prolongation of the dosing interval in any subsequent cohort will cease. As an additional safety precaution, if individual stopping rules (eg, due to AEs) are invoked in 10 of the first 20 subjects to enroll in any cohort, further enrollment in that cohort will cease. Finally, the SMC retains the authority to stop further enrollment into a cohort at any time for any reason. If any of these conditions transpire, all remaining subjects, including those ongoing subjects in the terminated cohort, and future subjects, will be administered AR101 300 mg at the longest interval tolerated by a previous cohort.

*Assumptions = Up to approximately 500 ARC003 completers (having received active or placebo in ARC003 at a 3:1 ratio) are projected for recruitment into ARC004. This assumes a loss of 15% of the randomized ARC003 population due to attrition, AEs, etc. Thus, the planned sizes for the ARC004 cohorts is as follows, though the actual number may vary due to recruitment:

- Cohort 1 = 120, prespecified
- Cohort 2 = 50, prespecified
- Cohort 3 = 175, distributed equally across Cohorts 3A, 3B, 3C
- Group 1 = 130 (25% of ARC003 enrollment, accounting for 5% dropout)

8 OPTIONAL MECHANISTIC STUDIES

Subjects from selected centers in ARC004 are eligible to participate in the optional collections of saliva and peripheral blood specimens to be collected for future studies designed to better understand the biological basis and treatment of food allergy. These additional specimens are entirely voluntary, do not affect the subject's participation in ARC004, and require separate informed consent. The additional tubes of peripheral blood are to be collected at the same time points as the routine laboratory work in ARC004 and do not require additional visits or phlebotomy. The saliva specimens will be collected as part of an ongoing collaboration with researchers at Cincinnati Children's Hospital Medical Center to analyze the salivary mRNA transcriptome of participants receiving OIT, as outlined further in Appendix 6.

9 STATISTICAL CONSIDERATIONS

This protocol outlines the major statistical considerations for the ARC004 study. Full details on the statistical methodology to be used in the analysis and data handling for this trial will be described in the statistical analysis plan (SAP) to be developed prior to database lock and statistical analysis.

Data will be summarized using descriptive statistics within treatment group and cohort. No specific hypothesis testing or comparisons between the treatment groups is planned for this study. Details of within group and within cohort comparisons relative to baseline values and exploratory comparisons between cohorts will be described in the SAP.

Descriptive statistics will be presented in the following manner:

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

Data will be summarized by treatment group, cohort, and treatment phase (as defined in Section 3.1).

Data will be summarized in tables for each treatment group, treatment groups combined, and treatment phase (as defined in Section 3.1).

Data from ARC003 will be combined with ARC004 and will be used to define baseline, as appropriate. Additional details about combining data and handling varying exposure times will be described in the SAP. Data will be listed for each subject.

9.1 Analysis Populations

The primary population of analysis for all analyses will be the Safety population. The Safety population will consist of all subjects who receive study treatment during ARC004.

A Per Protocol (PP) population, limited to subjects who have no major protocol deviations and who undergo Exit DBPCFC, may be defined. Exclusions will be determined by data review and documented before database lock.

Additional analysis populations may be defined in the SAP.

9.2 Study Endpoints

9.2.1 Primary Endpoint

The primary endpoint is the frequency of treatment-related AEs, including SAEs, during the overall study period (from enrollment to the end of EM).

9.2.2 Secondary Endpoints

- Frequency of anaphylaxis
- Frequency of use of epinephrine as a rescue medication
- Frequency of AEs leading to withdrawal of AR101
- Frequency of AEs in each treatment regimen leading to discontinuation of extended interval dosing
- Frequency of GI AEIs
- Frequency of accidental food allergen exposure
- In subjects with asthma, change in asthma control using the Asthma Control Test questionnaire (see Appendix 2)
- Frequency of all above safety endpoints by treatment period
- The proportion of subjects in each regimen tolerating ≥ 1043 mg cumulative of peanut protein during their EM Exit DBPCFC
- The proportion of subjects in each regimen who tolerate ≥ 443 mg cumulative of peanut protein during their EM Exit DBPCFC
- The proportion of subjects in each regimen who tolerate 4043 mg cumulative of peanut protein during their EM Exit DBPCFC

- Maximum tolerated dose and change from baseline* at Post-Maintenance** and each EM Exit DBPCFC
- Maximum severity of symptoms at each challenge dose at Post-Maintenance** and each EM Exit DBPCFC
- Frequency of use of epinephrine as a rescue medication at the Post-Maintenance** and each EM Exit DBPCFC
- Change in QoL as assessed by the FAQLQ and the FAIM questionnaire
- Satisfaction with AR101 treatment as assessed by the TSMQ-9 questionnaire and additional questions
- Changes in peanut-specific serum IgE and IgG4 levels
- Changes in peanut skin prick test (SPT) wheal diameter

*Baseline is defined as the Screening DBPCFC from ARC003 for both treatment groups.

**Post-Maintenance is defined as the ARC003 Exit DBPCFCs for Group 2.

9.3 Subject and Demographic Data

9.3.1 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic data, collected from ARC003 and/or ARC004 will be provided for all enrolled subjects. Baseline and 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.

9.3.2 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.

9.3.3 Study Disposition

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

9.3.4 Adverse Events

Adverse events will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Events will be tabulated by system organ classification and preferred term. Selected summaries will also be prepared by severity and relationship to

study treatment. An Adjudication Committee will be convened for this study. The committee will adjudicate all SAEs and AEIs. Both the investigator and the adjudicated assessments will be reported in the clinical study report.

9.4 Sample Size and Power Calculations

The primary objective of this study is to determine the safety, tolerability, and efficacy of AR101 CODIT using alternative maintenance dosing intervals. The sample size for this study is based on the number of eligible subjects from study ARC003 consenting to rollover into the ARC004 open-label protocol.

ARC003 had a target enrollment of 500 and a 3:1 AR101:placebo randomization ratio, providing 89% power to rule out a treatment difference (AR101 minus placebo) of 15% or less at the primary endpoint of the proportion of subjects who tolerate ≥ 1043 mg cumulative of peanut protein with no more than mild symptoms at the Exit DBPCFC. Assuming accrual of 80% of the total ARC003 sample into ARC004, the total of approximately 400 subjects treated with AR101 in the clinical program would provide an 80% probability of observing ≥ 1 AE when the background rate of the AE is 4 per 1,000 subjects.

There is no prospective power calculation for efficacy in ARC004.

10 IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 Web-Based Data Collection and Management System

Data collection will occur via a web-based data entry system to allow easy access to enrollment 24 hours a day, 7 days a week. Upon enrollment, a form submission schedule is generated for each subject that permits direct access to each eCRF 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 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 retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified, or longer if required by local regulations.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Statement of Compliance

This study will be conducted using good clinical practice (GCP), as delineated in 21 CFR Parts 50, 54, 56, and 312 and in the ICH "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance," national and international regulations and directives as appropriate, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB/EC and other applicable health authorities. Any amendments to the protocol must also be approved by Aimmune Therapeutics, IRB/EC, and other applicable health authorities before they are implemented. Any amendments to the consent materials must also be approved by Aimmune Therapeutics and IRB/EC before they are implemented.

11.2 Informed Consent/Assent

The informed consent 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 comprise a significant percentage of children, parents or legal guardians will be asked to read, sign, and date a consent form before a child enters the study, takes study product, or undergoes any study-specific procedures. When required, both parents will sign the consent form before a child can be enrolled in the study. Children will be asked to sign an assent as appropriate. Consent materials for subjects or 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 form will be given to a prospective subject or parent/guardian for review. The investigator (or designee), will review the consent and answer questions, as well as emphasize the need to avoid allergen exposure other than to AR101, and the necessity to continue exposure to AR101 to maintain desensitization. The prospective 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. 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 are the property of the Sponsor and will be sent to the Sponsor or designee for storage and analysis. Subject data will be anonymized to maintain subject confidentiality. All data sets will be archived by the Sponsor or designee and may be made available to interested, outside investigators with approval by the Sponsor.

The Sponsor will review and approve any abstracts or manuscripts prepared from these data prior to their submission.

13 PROTOCOL DEVIATIONS

The investigators and site staff will conduct the study in accordance with the protocol. Any departure from the study design or procedures constitutes a protocol deviation.

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

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

13.1 Reporting and Managing Protocol Deviations

The Principal Investigator has the responsibility to identify, document and report protocol deviations. When necessary, the Investigator can implement a deviation to the protocol in order to eliminate an immediate hazard to a study subject; however, every effort should be made to discuss this with the Sponsor's Medical Monitor before doing so. Protocol deviations may also be identified during site monitoring visits or other reviews of study conduct. All protocol deviations will be reported in the clinical database.

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

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

Protocol deviations must be clearly documented, including the reason for them. If protocol deviations lead to the protocol being amended, the amended protocol will be submitted to the relevant IRB/IEC and Regulatory Authorities for review, as appropriate.

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Appendix 1: Schedules of Events

Appendix 1-A: Schedule of Events for Group 1 and Subjects Switching to Daily Dosing

Visit		Screening/ Baseline	Initial Escalation	Up-dosing/ Repeat Up-Dosing[a]				Initial Maintenance[a]	Unscheduled[b]
				CRC Up-dosing Visits (not 80 mg, 300 mg, or End of Up-dosing)	80 mg Visit	300 mg Visit	End of Up-dosing/ Maintenance Visit 1	CRC Dosing Maintenance Visits 2 and 3	
			Up to 10 days after Screening/ Baseline[c]	~every 2 wks for 22-40 wks[d]	~Week 10	≤ Week 40	2 Weeks after Reaching 300 mg/d	Weeks 12, 24[e]	Investigator Discretion
Informed consent/assent		X							
Inclusion/exclusion criteria		X							
Medical/allergy history		X							
Diet (food allergen) history		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X
Physical examination[f]		X	X	X	X	X	X[g]	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[h]		X	X	X	X	X	X	X	X
Pregnancy test[i]		Serum			Urine		Urine		Urine
FAQLQ & FAIM questionnaire[j]		X							
TSQM-9 and Exit questionnaire[k]									
Blood draw	Peanut-specific IgE, IgG4[l]	X					X	X[x]	X
	CBC	X					X	X[x]	X
	Optional extra volume for exploratory immune studies at selected centers[m]	X					X	X[x]	X

Visit	Screening/ Baseline	Initial Escalation	Up-dosing/ Repeat Up-Dosing[a]				Initial Maintenance[a]	Unscheduled[b]
			CRC Up-dosing Visits (not 80 mg, 300 mg, or End of Up-dosing)	80 mg Visit	300 mg Visit	End of Up-dosing/ Maintenance Visit 1	CRC Dosing Maintenance Visits 2 and 3	
		Up to 10 days after Screening/ Baseline[c]	~every 2 wks for 22-40 wks[d]	~Week 10	≤ Week 40	2 Weeks after Reaching 300 mg/d	Weeks 12, 24[e]	Investigator Discretion
Optional saliva collection at selected centers								
No GI symptoms (controls)	X		X[o]			X		
GI symptoms (cases)	X		X[o]					X[o]
Skin prick test	X					X	X[x]	X
Administration of OIT at site[p]		X	X	X	X	X	X[w]	X
Dispense / return unused study product		X	X	X	X	X	X	X
DBPCFC (2 parts within 7 days)	X						X[q,r]	
Monitor AEs/allergic symptoms[s]	X	X	X	X	X	X	X	X
Monitor for compliance	X		X	X	X	X	X	X
Assessment of asthma (including ACT)	X			X		X	X	X
Subject reminder to avoid peanut; allergy training	X	X	X	X	X	X	X	X
Telephone follow-up[t,u]		X	X	X	X	X	X	X
PEESS v2.0 questionnaire								X[v]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo controlled food challenge; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR = peak expiratory flow rate; PR = pulse rate; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; wks = weeks

Footnotes:

a) Subjects who have the option to switch to AR101 daily in ARC008 may start AR101 daily dosing (Repeat Up-dosing from 80, 120, or 160 mg to 300 mg daily) and have visits in ARC004 if ARC008 is not yet available at the study site (Section 3). Repeat Up-dosing may be up to a maximum of 26 weeks.

b) Any of the procedures performed at CRC dosing visits (except Post-Maintenance DBPCFC) may be performed at unscheduled visits.

c) Day 1 of the Initial Escalation Period will be scheduled within 10 days after the ARC003 Exit DBPCFC. See Table 1 for dose escalation schedule. Subjects will begin home dosing at dose 3 mg/d on Day 3.
   – Day 1: Escalation to ≥ 3 mg or 6 mg, as tolerated (subjects who cannot tolerate 3 mg are escalation failures).
   – Day 2: Confirm tolerance of 3 mg. Day 2 should occur on the next consecutive day following Day 1.

d) Subjects return to clinic every 2 weeks for up-dosing to a maximum of 300 mg, following the dose escalation schedule in Table 2, unless up-dosing is delayed due to allergic reaction. The Up-dosing Period ends after maintaining the 300-mg dose for 2 weeks.

e) CRC dosing occurs at Weeks 12 and 24 after entering the Maintenance Period, with a Post-maintenance DBPCFC at Week 24 (approximately).

f) Physical examination to include height and weight. At the investigator's discretion, limited or symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline, 80 mg Up-dosing Visit, End of Up-dosing/Maintenance Visit 1 (2 weeks at 300 mg), and the Exit/Early Discontinuation visits.

g) End of Up-dosing/Maintenance Visit 1 physical examination will be a complete physical examination and will include height and weight.

h) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.

i) For females of childbearing potential.

j) FAQLQ and FAIM questionnaires to be filled out after ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.

k) TSQM-9 and Exit questionnaires to be answered after Exit DBPCFC.

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

m) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.

n) Blood draw to be collected prior to the Exit DBPCFC.

o) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva sub-study will be allowed to enroll upon early termination.

p) The first 2 twice weekly (BIW), once weekly (QW), and every other week (QOW) doses (as applicable) administered to Group 1 during the Extended Maintenance Period will be in clinic.

q) Post-Maintenance DBPCFC to 2000 mg (4043 cumulative) peanut protein is performed only at the end of the 24 week 300 mg Maintenance Period (not at each CRC dosing visit).

r) DBPCFC to 2000 mg (4043 mg cumulative) peanut protein at Exit visit only.

s) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. GI AEIs will be monitored according to Section 7.3.3.2.

t) Telephone follow-up will occur 1 day after each escalation visit and Initial Maintenance visit to inquire about allergic symptoms and promote compliance.

u) Telephone follow-up will occur 6 weeks before and after each scheduled Initial Maintenance visit to inquire about allergic symptoms and promote compliance.

v) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   - Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   - Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   - Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

w) Subjects should not administer their AR101 dose on days when DBPCFC is conducted.

x) For group 1 subjects only. Perform before the Post-Maintenance DBPCFC at the end of Initial Maintenance.

Appendix 1-B: Schedule of Events for Group 1 and Subjects Switching to Daily Dosing (Continued)

Visit		Ext Maint	Ext Maint Visits 2a / 2b (Initiation Visit Day 1 and 2)		Ext Maint Visits 3a / 3b (Initiation Visit Day 1 and 2)		Ext Maint Visits 4a / 4b (Initiation Visit Day 1 and 2)		Exit / Early Discontinuation	Unscheduled[a]
			~8-24 wks at BIW +/- 1 wk		~8-24 wks at QW +/- 1 wk		~8-24 weeks at QOW +/- 1 wk			
Dosing Interval		**QD**	**Begin BIW**		**Begin QW**		**Begin QOW**			
Informed consent/assent										
Inclusion/exclusion criteria										
Medical/allergy history										
Diet (food allergen) history		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Physical examination[b]		X	X	X	X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X	X	X	X	X
Pregnancy test[d]		Urine	Urine		Urine		Urine		Urine	Urine
FAQLQ & FAIM questionnaire[e]									X	
TSQM-9 and Exit questionnaire									X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]		X		X		X		X	X
	CBC		X		X		X		X	X
	Optional extra volume for exploratory immune studies at selected centers[h]		X[i]		X[i]		X[i]		X[i]	X
Optional saliva collection at selected centers No GI symptoms (controls) GI symptoms (cases)									 X[j]	
Skin prick test			X		X		X		X	X
Administration of OIT at site		X[k,l]	X	X	X	X	X	X		X
Dispense / return unused study product[m]		X	X	X	X	X	X	X	X	X

Visit	Ext Maint	Ext Maint Visits 2a / 2b (Initiation Visit Day 1 and 2)		Ext Maint Visits 3a / 3b (Initiation Visit Day 1 and 2)		Ext Maint Visits 4a / 4b (Initiation Visit Day 1 and 2)		Exit / Early Discontinuation	Unscheduled[a]
		~8-24 wks at BIW +/- 1 wk		~8-24 wks at QW +/- 1 wk		~8-24 weeks at QOW +/- 1 wk			
Dosing Interval	**QD**	**Begin BIW**		**Begin QW**		**Begin QOW**			
DBPCFC (2 parts within 7 days)								X[n,o]	
Monitor AEs/allergic symptoms[p]	X	X	X	X	X	X	X	X	X
Monitor for compliance	X	X		X		X		X	X
Assessment of asthma (ACT)	X	X		X		X		X	X
Subject reminder to avoid peanut; allergy training	X	X	X	X	X	X	X	X	X
Telephone follow-up[q,r]	X	X	X	X	X	X	X		X
PEESS v2.0 questionnaire								X[s]	X[s]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BIW = biweekly; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; EM, Extended Maintenance Period; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR= peak expiratory flow rate; PR = pulse rate; QD = once daily; QOD = every other day; QOW = every other week; QW = once weekly; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; wk = week

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.

b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Exit/Early Discontinuation (Termination) visit.

c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.

d) For females of childbearing potential.

e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.

f) TSQM-9 and Exit questionnaires to be answered after exit DBPCFC.

g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.
i) Blood draw to be collected prior to the Exit DBPCFC.
j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva sub-study will be allowed to enroll upon early termination.
k) The first 2 BIW, QW, and QOW doses (as applicable) administered during EM to Group 1 will be in clinic.
l) Day 1 of the Initial Escalation Period will be scheduled within 10 days after the ARC003 Exit DBPCFC. See Table 1 for dose escalation schedule. Subjects will begin home dosing at dose 3 mg/d on Day 3.
   – Day 1: Escalation to ≥ 3 mg or 6 mg, as tolerated (subjects who cannot tolerate 3 mg are escalation failures).
   – Day 2: Confirm tolerance of 3 mg. Day 2 should occur on the next consecutive day following Day 1.
m) Subjects return to clinic every 2 weeks for up-dosing to a maximum of 300 mg, following the dose escalation schedule in Table 2, unless up-dosing is delayed due to allergic reaction.
n) Post-Maintenance DBPCFC to 2000 mg (4043 cumulative) peanut protein is performed only at the end of the CRC 300 mg dosing period (not at each CRC dosing visit).
o) DBPCFC to 2000 mg (4043 mg cumulative) peanut protein at Exit visit only. For subjects who do not tolerate their nondaily dosing regimen and subjects who switch to daily dosing after missing their nondaily dose for > 3 days, the exit DBPCFC will be omitted before discontinuation from ARC004 and enrollment in ARC008.
p) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. GI AEIs will be monitored according to Section 7.3.3.2.
q) Telephone follow-up will occur 1 day after each EM visit to inquire about allergic symptoms and promote compliance.
r) Telephone follow-up will occur 7 weeks before and after each scheduled EM follow-up visit to inquire about allergic symptoms and promote compliance.
s) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   – Any subject whose dose is withheld for >7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   – Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   – Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 1-C: Schedule of Events for Group 2, Cohort 1

Visit		Screening/ Baseline Visit Days 1-3	Ext Maint ~Week 14 (+/- 1 week)	Exit Visit ≥ Week 28	Early Discontinuation Visit	Unscheduled[a]
Dosing Interval		**QD Dosing**				
Informed consent/assent		X				
Inclusion/exclusion criteria		X				
Medical/allergy history		X				
Diet (food allergen) history		X	X	X	X	X
Concomitant medications		X	X	X	X	X
Physical examination[b]		X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X
Pregnancy test[d]		Serum		Urine	Urine	Urine
FAQLQ & FAIM questionnaire[e]		X		X	X	
TSQM-9 and Exit questionnaire				X[f]	X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]	X		X	X	X
	CBC	X		X	X	X
	Optional extra volume for exploratory immune studies at selected centers[h]	X		X[i]	X[i]	X
Optional saliva collection at selected centers						
	No GI symptoms (controls)	X				
	GI symptoms (cases)	X		X[j]	X[j]	
Skin prick test		X		X	X	X
Administration of OIT at site			X			X
Dispense / return unused study product		X[k]	X	X[k]	X	X
DBPCFC (2 parts within 7 days)		X		X		
Monitor AEs / allergic symptoms[l]		X	X	X	X	X
Monitor for compliance			X	X	X	X
Assessment of asthma (ACT)		X	X	X	X	X
Subject reminder to avoid peanut; allergy training		X	X	X	X	X

Visit	Screening/ Baseline Visit Days 1-3	Ext Maint ~Week 14 (+/- 1 week)	Exit Visit ≥ Week 28	Early Discontinuation Visit	Unscheduled[a]
Dosing Interval	**QD Dosing**				
Telephone Follow-up		X[m]			
PEESS v2.0 questionnaire			X[n]	X[n]	X[n]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR= peak expiratory flow rate; PR = pulse rate; QD = once daily; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.
b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline and the Exit/Early Discontinuation (Termination) visits.
c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
d) For females of childbearing potential.
e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.
f) TSQM-9 and Exit questionnaires to be answered after exit DBPCFC.
g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.
i) Blood draw to be collected prior to the Exit DBPCFC.
j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination.
k) Until ARC008 is available, an additional AR101 14-week supply may be dispensed at this visit.
l) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. Gastrointestinal AEIs will be monitored according to Section 7.3.3.2.
m) Telephone follow-up will occur 7 weeks before and after this visit (ie, Weeks 7 and 21) to inquire about allergic symptoms and promote compliance.

n) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   - Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   - Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   - Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 1-D: Schedule of Events for Group 2, Cohort 2

Visit		Screening/ Baseline Visit Days 1-3	Initiation Visit Day 1 2-4 Days after Last QOD Dose	Initiation Visit Day 2 2-4 Days after Initiation Visit Day 1	Ext Maint ~Week 14 (+/- 1 week)	Exit Visit ~Week 28	Early Discontinuation	Unscheduled [a]
Dosing Interval			**Begin BIW**	**BIW Dosing**				
Informed consent/assent		X						
Inclusion/exclusion criteria		X						
Medical/allergy history		X						
Diet (food allergen) history		X			X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Physical examination[b]		X	X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X	X	X
Pregnancy test[d]		Serum				Urine	Urine	Urine
FAQLQ & FAIM questionnaire[e]		X				X	X	
TSQM-9 and Exit questionnaire						X[f]	X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]	X			X	X	X	X
	CBC	X			X	X	X	X
	Optional extra volume for exploratory immune studies at selected centers[h]	X			X[i]	X[i]	X	X
Optional saliva collection at selected centers								
	No GI symptoms (controls)	X						
	GI symptoms (cases)	X				X[j]	X[j]	
Skin prick test		X	X		X	X	X	X
Administration of OIT at site			X[k]	X	X			X
Dispense / return unused study product		X		X	X	X	X	X
DBPCFC (2 parts within 7 days)		X				X		

Visit	Screening/ Baseline Visit Days 1-3	Initiation Visit Day 1 2-4 Days after Last QOD Dose	Initiation Visit Day 2 2-4 Days after Initiation Visit Day 1	Ext Maint ~Week 14 (+/- 1 week)	Exit Visit ~Week 28	Early Discontinuation	Unscheduled [a]
Dosing Interval		**Begin BIW**	**BIW Dosing**				
Monitor AEs / allergic symptoms[l]	X	X	X	X	X	X	X
Monitor for compliance				X	X	X	X
Assessment of asthma (ACT)	X			X	X	X	X
Subject reminder to avoid peanut; allergy training	X	X	X	X	X	X	X
Telephone follow-up		X	X	X[m]			
PEESS v2.0 questionnaire					X[n]	X[n]	X[n]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BIW = biweekly; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR = peak expiratory flow rate; PR = pulse rate; QOD = every other day; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.
b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline and the Exit/Early Discontinuation (Termination) visits.
c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
d) For females of childbearing potential.
e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.
f) TSQM-9 and Exit questionnaires to be answered after Exit DBPCFC.
g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.

i) Blood draw to be collected prior to the Exit DBPCFC.

j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination.

k) For Cohort 2, the first 2 BIW doses administered during Ext Maint will be in clinic. Doses should be at least 3 days apart (eg. Monday and Thursday each week)

l) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. Gastrointestinal AEIs will be monitored according to Section 7.3.3.2.

m) Telephone follow-up will occur 7 weeks before and after this visit (ie, Weeks 7 and 21) to inquire about allergic symptoms and promote compliance.

n) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
- Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 1-E: Schedule of Events for Group 2, Cohort 3A

Visit		Screening/ Baseline Days 1-3	Ext Maint 1 ~Week 14 +/- 1 wk	Ext Maint 2 ~Week 28 +/- 1 wk	Ext Maint 3 ~Week 42 +/- 1 wk	Exit Visit ~Week 56 +/- 1 wk	Early Discontinuation Visit	Unscheduled[a]
Dosing Interval		**QD Dosing**						
Informed consent/assent		X						
Inclusion/exclusion criteria		X						
Medical/allergy history		X						
Diet (food allergen) history		X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Physical examination[b]		X	X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X	X	X
Pregnancy test[d]		Serum		Urine		Urine	Urine	Urine
FAQLQ & FAIM questionnaire[e]		X				X	X	
TSQM-9 and Exit questionnaire						X[f]	X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]	X		X		X	X	X
	CBC	X		X		X	X	X
	Optional extra volume for exploratory immune studies at selected centers[h]	X		X		X[i]	X[i]	X
Optional saliva collection at selected centers								
	No GI symptoms (controls)	X						
	GI symptoms (cases)	X				X[j]	X[j]	
Skin prick test		X		X		X	X	X
Administration of OIT at site			X	X	X			X
Dispense / return unused study product		X	X	X	X	X	X	X
DBPCFC (2 parts within 7 days)		X				X		
Monitor AEs / allergic symptoms[k]		X	X	X	X	X	X	X

Visit	Screening/ Baseline Days 1-3	Ext Maint 1 ~Week 14 +/- 1 wk	Ext Maint 2 ~Week 28 +/- 1 wk	Ext Maint 3 ~Week 42 +/- 1 wk	Exit Visit ~Week 56 +/- 1 wk	Early Discontinuation Visit	Unscheduled[a]
Dosing Interval	**QD Dosing**						
Monitor for compliance		X	X	X	X	X	X
Assessment of asthma (including ACT)	X	X	X	X	X	X	X
Subject reminder to avoid peanut; allergy training	X	X	X	X	X	X	X
Telephone follow-up[l]		X		X			X
PEESS v2.0 questionnaire					X[m]	X[m]	X[m]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR = peak expiratory flow rate; PR = pulse rate; QD = once daily; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; wk = week.

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.
b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline and the Exit/Early Discontinuation (Termination) visits.
c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
d) For females of childbearing potential.
e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.
f) TSQM-9 and Exit questionnaires to be answered after Exit DBPCFC.
g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.
i) Blood draw to be collected prior to the Exit DBPCFC.
j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination.

k) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. Gastrointestinal AEIs will be monitored according to Section 7.3.3.2.

l) Telephone follow-up will occur 7 weeks before and after each in-clinic visit (ie, Weeks 7, 21, 35, 49, 63, 77, as applicable) to inquire about allergic symptoms and promote compliance.

m) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   - Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   - Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   - Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 1-F: Schedule of Events for Group 2, Cohort 3B

Visit		Screening/ Baseline	Ext Maint Visit 1	Ext Maint Visit 2	Ext Maint Visits 3a / 3b (Initiation Day 1 and 2)		Ext Maint Visit 4	Exit	Early Discontinuation	Unscheduled [a]
		Days 1-3	~Week 14 +/- 1 wk	~ Week 28 +/- 1 wk	~Week 32/33 +/- 1 wk		~Week 42 +/- 1 wk	~Week 56 +/- 1 wk		
Dosing Interval		**QD Dosing**		**Begin QOD**	**Begin BIW**		**BIW Dosing**			
Informed consent/assent		X								
Inclusion/exclusion criteria		X								
Medical/allergy history		X								
Diet (food allergen) history		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Physical examination[b]		X	X	X	X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X	X	X	X	X
Pregnancy test[d]		Serum		Urine				Urine	Urine	Urine
FAQLQ & FAIM questionnaire[e]		X						X	X	
TSQM-9 and Exit questionnaire								X[f]	X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]	X		X				X	X	X
	CBC	X		X				X	X	X
	Optional extra volume for exploratory immune studies at selected centers[h]	X		X				X[i]	X[i]	X
Optional saliva collection at selected centers										
	No GI symptoms (controls)	X								
	GI symptoms (cases)	X						X[j]	X[j]	
Skin prick test		X		X	X		X	X	X	X
Administration of OIT at site[k]			X	X	X	X	X			X

Visit	Screening/ Baseline	Ext Maint Visit 1	Ext Maint Visit 2	Ext Maint Visits 3a / 3b (Initiation Day 1 and 2)		Ext Maint Visit 4	Exit	Early Discontinuation	Unscheduled [a]
	Days 1-3	~Week 14 +/- 1 wk	~ Week 28 +/- 1 wk	~Week 32/33 +/- 1 wk		~Week 42 +/- 1 wk	~Week 56 +/- 1 wk		
Dosing Interval	**QD Dosing**		**Begin QOD**	**Begin BIW**		**BIW Dosing**			
Dispense / return unused study product	X	X	X	X	X	X	X	X	X
DBPCFC (2 parts within 7 days)	X						X		
Monitor AEs / allergic symptoms[l]	X	X	X	X	X	X	X	X	X
Monitor for compliance		X	X	X	X	X	X	X	X
Assessment of asthma (including ACT)	X	X	X	X		X	X	X	X
Subject reminder to avoid peanut; allergy training	X	X	X	X	X	X	X	X	X
Telephone follow-up[m]		X	X			X			X
PEESS v2.0 questionnaire							X[n]	X[n]	X[n]

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BIW = biweekly; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR = peak expiratory flow rate; PR = pulse rate; QD = once daily; QOD = every other day; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; wk = week

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.

b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline and the Exit/Early Discontinuation (Termination) visits.

c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.

d) For females of childbearing potential.
e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.
f) TSQM-9 and Exit questionnaires to be answered after Exit DBPCFC.
g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.
i) Blood draw to be collected prior to the Exit DBPCFC.
j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination.
k) The first 2 BIW doses administered during Ext Maint to Cohort 3B will be in clinic. BIW doses should be at least 3 days apart (eg. Monday and Thursday each week).
l) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. Gastrointestinal AEIs will be monitored according to Section 7.3.3.2.
m) Telephone follow-up will occur 7 weeks before and after each in-clinic visit (ie, Weeks 7, 21, 35, 49, 63, 77, as applicable) to inquire about allergic symptoms and promote compliance.
n) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   – Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   – Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   – Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 1-G: Schedule of Events for Group 2, Cohort 3C

Visit		Screening / Baseline	Ext Maint Visit 1	Ext Maint Visit 2	Ext Maint Visits 3a / 3b (Initiation Visit Day 1 and 2)		Ext Maint Visit 4	Ext Maint Visits 5a / 5b (Initiation Visit Day 1 and 2)		Ext Maint Visit 6	Exit Visit	Early Discontinuation	Unscheduled [a]
		Days 1-3	~Week 14 +/- 1 wk	~Week 28 +/- 1 wk	~Week 32/33 +/- 1 wk		~Week 42 +/- 1 wk	~Wk 56/57 +/- 1 wk		~Week 70 +/- 1 wk	~Week 84 +/- 1 wk		
Dosing Interval		QD Dosing		Begin QOD	Begin BIW		BIW Dosing	Begin QW		QW Dosing			
Informed consent/assent		X											
Inclusion/exclusion criteria		X											
Medical/allergy history		X											
Diet (food allergen) history		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X	X	X	X	X	X	X	X	X	X	X
PEFR/Spirometry (FEV_1)[c]		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[d]		Serum		Urine				Urine			Urine	Urine	Urine
FAQLQ & FAIM questionnaire[e]		X									X	X	
TSQM-9 and Exit questionnaire											X[f]	X[f]	
Blood draw	Peanut-specific IgE, IgG4[g]	X		X				X			X	X	X
	CBC	X		X				X			X	X	X
	Optional extra volume for exploratory immune studies at selected centers[h]	X		X				X[i]			X[i]	X[i]	X
Optional saliva collection at selected centers													
	No GI symptoms (controls)	X											
	GI symptoms (cases)	X									X[j]	X[j]	

Visit	Screening / Baseline	Ext Maint Visit 1	Ext Maint Visit 2	Ext Maint Visits 3a / 3b (Initiation Visit Day 1 and 2)		Ext Maint Visit 4	Ext Maint Visits 5a / 5b (Initiation Visit Day 1 and 2)		Ext Maint Visit 6	Exit Visit	Early Discontinuation	Unscheduled [a]
	Days 1-3	~Week 14 +/- 1 wk	~Week 28 +/- 1 wk	~Week 32/33 +/- 1 wk		~Week 42 +/- 1 wk	~Wk 56/57 +/- 1 wk		~Week 70 +/- 1 wk	~Week 84 +/- 1 wk		
Dosing Interval	**QD Dosing**		**Begin QOD**	**Begin BIW**		**BIW Dosing**	**Begin QW**		**QW Dosing**			
Skin prick test	X		X	X		X	X		X	X	X	X
Administration of OIT at site[k]		X	X	X	X	X	X	X	X			X
Dispense / return unused study product	X	X	X	X	X	X	X	X	X	X	X	X
DBPCFC (2 parts within 7 days)	X									X		
Monitor AEs / allergic symptoms[l]	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for compliance		X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma (including ACT)	X	X	X	X		X	X		X	X	X	X
Reminder to avoid peanut; allergy training	X	X	X	X	X	X	X	X	X	X	X	X
Telephone follow-up[m]		X	X			X	X		X			X
PEESS v2.0 questionnaire										X^{n}	X^{n}	X^{n}

Abbreviations: ACT = Asthma Control Test; AEs = adverse events; AEIs = adverse events of interest; BIW = biweekly; BP = blood pressure; CBC = complete blood count; CRC = clinical research center; DBPCFC = double-blind, placebo-controlled food challenge; Ext Maint = Extended Maintenance Period; FAIM = food allergy independent measure; FAQLQ = food allergy related quality of life questionnaire; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; Ig = immunoglobulin; OIT = oral immunotherapy; PEESS = Pediatric Eosinophilic Esophagitis Symptom Scores; PEFR = peak expiratory flow rate; PR = pulse rate; QD = once daily; QOD = every other day; QW = once weekly; temp = body temperature; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; wk = week

Footnotes:

a) Any of the procedures performed at CRC dosing visits may be performed at unscheduled visits.

b) Physical examination to include height and weight. At the investigator's discretion, symptom-directed physical examinations may be completed in CRC dosing visits during the Extended Maintenance Period. Full physical examinations are to be conducted at the Screening/Baseline and the Exit/Early Discontinuation (Termination) visits.

c) PEFR to be performed in all subjects 6 years of age or older, measured at approximately the same time for each assessment visit; 3 attempts of PEFR should be performed, and the best attempt selected. For subjects 4 or 5 years of age, PEFR is to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required. Spirometry (FEV_1) is to be performed in subjects 6 years of age or older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination.); 3 attempts of FEV_1 should be performed, and the best attempt selected. In order to assess whether the subject is able to adequately perform spirometry, the spirometry must be attempted, and any attempt must be documented.
d) For females of childbearing potential.
e) FAQLQ and FAIM questionnaires to be filled out prior to ARC003 Exit DBPCFC and after ARC004 Exit DBPCFC.
f) TSQM-9 and Exit questionnaires to be answered after Exit DBPCFC.
g) Blood for peanut-specific IgE, IgG4 to be drawn prior to DBPCFC.
h) Optional blood draw at selected centers according to local institutional guidelines for minimal risk phlebotomy procedures in children. No more than 50 mL total within 8 weeks may be drawn.
i) Blood draw to be collected prior to the Exit DBPCFC.
j) Subjects withdrawing early from ARC004 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination.
k) The first 2 BIW and QW doses administered during Ext Maint to Cohort 3C will be in clinic. BIW doses should be at least 3 days apart (eg. Monday and Thursday each week). QW doses should be taken on the same day (± 1 day) each week.
l) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the Early Discontinuation Visit, whichever comes first. Gastrointestinal AEIs will be monitored according to Section 7.3.3.2.
m) Telephone follow-up will occur 7 weeks before and after each in-clinic visit (ie, Weeks 7, 21, 35, 49, 55, 63, 77, as applicable) to inquire about allergic symptoms and promote compliance.
n) Subjects who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   - Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2).
   - Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 6.5.3.2).
   - Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2).

Appendix 2: Evaluation of Asthma

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

Table: National Heart, Lung, and Blood Institute (NHLBI) Classification

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

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

FEV_1 = forced expiratory volume in the first second of expiration; FVC = forced vital capacity.

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

Criteria for Suspected Diagnosis

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

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

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

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

Table: Criteria for Severity Grading

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

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

Appendix 4: Allergic Reaction Severity Grading

The Consortium of Food Allergy Research (CoFAR) grading system for allergic reactions is displayed in the table below.

Table: CoFAR Specific Grading System for Allergic Reactions

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

For an episode of anaphylaxis to be considered a serious adverse event (SAE), Aimmune Therapeutics advises that the event satisfy one of the outcome-based definitions of SAE specified in Section 7.3.2.

In this protocol, with the stipulations (denoted in *italics*) indicated, these stipulations follow from, and are consistent with, the criteria for safety monitoring committee (SMC) reporting (Section 7.5.2):

1. Death – *No further stipulation.*
2. Life-threatening adverse event (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 Appendix 4.*
3. Inpatient hospitalization or prolongation of existing hospitalization: *The hospital admission should not have been solely for the sake of providing an extended period of observation, as, for example, might be implemented to watch for a delayed or biphasic reaction.*
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: *No further stipulation.*
5. Congenital abnormality or birth defect: *No further stipulation.*
6. Important medical event that may not result in 1 of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event:
   - *In general, for an anaphylactic episode to be classified as an SAE based on 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 intravenous epinephrine, intubation, or admission to an intensive care unit.*
   - *One or 2 intramuscular injections of epinephrine should ordinarily not be construed as intensive therapy*
   - *If an investigator assesses an episode of anaphylaxis to be an "important medical event" when the episode was of mild or moderate severity and did not require intensive therapy, the rationale for the assessment must be explained in detail in the narrative of the event.*

Appendix 6: Exploratory Biochemical and Molecular Substudy of Peanut-Allergic Children and Adults with Oral Immunotherapy-related Gastrointestinal Symptoms in Study ARC004

Background

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

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

In OIT studies, gastrointestinal adverse events (GI AEs) are typically prominent (Anagnostou et al, 2014; Yu et al, 2012; Blumchen et al, 2010; Jones et al, 2009) and account for a substantial proportion of premature discontinuations of study treatment (Burks et al, 2012; Varshney et al, 2011; Jones et al, 2009; Vickery et al, 2011). This was also observed in the completed ARC001 study and the ongoing ARC002 study. In the ARC001 study, 6 out of 29 subjects (21%) receiving active treatment discontinued prematurely. Four of the early discontinuations were attributed by the Principal Investigators to have been the consequence of recurrent GI AEs; in 1 of these cases the diagnosis of EoE was subsequently established by endoscopic biopsy. In the other 3 discontinuations, ≥ 1 GI AE had occurred in each subject. In the ongoing ARC002 study, an open-label follow-on to the ARC001 study, 6 of the 26 subjects (22%) who had been assigned to the placebo group in ARC001 discontinued therapy prematurely. Four of these early discontinuations were due to recurrent GI AEs and 2 were due to study visit scheduling difficulties.

Repeated bouts of abdominal pain and vomiting are common to both EoE and chronic/recurrent OIT-related GI symptoms, suggesting a common, or at least a similar, etiology in at least a proportion of patients. To date, ≥ 20 occurrences of OIT-related GI AEs have been confirmed histopathologically to be EoE as reported in the medical literature (Hofmann et al, 2009; Vickery et al, 2011; Wasserman et al, 2011; Sánchez-García et al,

2012; Lucendo et al, 2014), and in still other cases the symptomatology and clinical course (with or without concomitant blood eosinophilia) have been highly suggestive of EoE (Narisety et al, 2009; Vickery et al, 2011). A recent review of the literature (Lucendo et al, 2014) has indicated that the incidence of confirmed EoE in OIT is on the order of 3% (ranging from approximately 1% to 5%), but the incidence of suspected EoE on clinical grounds may be in the vicinity of 15 to 25%.

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

Chronic GI AEs affecting participants in ARC003 and ARC004 have been designated as adverse events of interest (AEIs) in the ARC003 and ARC004 protocols. The goal of the current substudy is to explore the biology of these GI AEIs occurring during exposure to study product using a readily available and noninvasive sampling method (saliva) in an attempt to overcome some of the difficulties in assessing intolerable GI AEs in subjects undergoing OIT.

Rationale for the Proposed Study

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

Specifically, this substudy of ARC004 will enroll all willing volunteers at screening and then collect further information from those subjects who go on to experience GI side effects during OIT, and controls. To overcome the obstacles limiting traditional EoE evaluations in this context (eg, performance of an esophagogastroduodenoscopy [EGD]), an easily collected biospecimen will be analyzed to determine whether patterns can be detected that correlate with patterns seen in other subjects with known bona fide EoE. As there are no known clinical predictors of EoE, all ARC004 participants will be approached about participating in this substudy, including those who may have participated in it during ARC003. Further analyses will be conducted on those subjects who develop GI symptoms during the course of OIT and controls who do not develop GI symptoms. While all subjects who consent to participate will provide baseline saliva specimens (collected at screening), we will be opportunistic about the collection of esophageal specimens, which may provide additional supportive data. Specifically, if subjects in the study withdraw from OIT and undergo a

clinically-indicated EGD, we will, whenever possible, collect biopsy material from the site for further analysis, as per the ARC004 protocol.

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

Known and Potential Risks and Benefits to Human Participants

Risks

The principal potential risk associated with this substudy is the potential for emotional or psychological distress related to the discovery of uncertain information that is not itself diagnostic but may suggest a new clinical diagnosis (ie, EoE). To mitigate against this risk, and because the assays run in this substudy are experimental, exploratory, and not part of standard care EoE diagnostics, the results of these studies will not be shared with participants. Clinical management of these individuals will be at the judgment of the site investigator, per the current standard of care. The ARC004 protocol also contains specific recommendations about the clinical follow-up of subjects developing AEIs. All study candidates entering ARC004 will undergo an informed consent procedure detailing the potential risk of OIT-associated GI symptoms, including the possibility of EoE.

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

Benefits

Individual subjects are not expected to benefit from participation in this study. Information from this study may help researchers to better understand peanut allergy and its relationship to EoE or to develop future tests or treatments to help patients with 1 or both conditions.

Objectives

Primary Objective

The primary objective is to analyze biomolecular expression patterns in saliva samples obtained longitudinally from peanut-allergic participants undergoing OIT in ARC004. These studies will target the salivary RNA transcriptome, and if necessary further validate, with molecular-, cellular-, and/or protein-based approaches, the expression profile of gene pathways that are likely relevant to intolerable GI side effects in ARC004 subjects.

Secondary Objectives

The key secondary objective is to examine the relationship of the RNA expression profile to selected clinical variables from ARC004, including:

- The frequency and severity of AEs related to the GI tract
- The frequency of dosing interruptions (reductions and/or discontinuations) directly related to GI AEs
- Peripheral blood eosinophil counts
- Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS) v2.0 scores
- Immunoglobulin levels (IgE, IgG4, and their subclasses)

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

Substudy Design

This is an optional substudy in which samples will be obtained from ARC004 participants according to the Schedule of Events for the substudy in the table below. Only subjects enrolled at selected centers in ARC004 and providing additional consent for this substudy are eligible to participate. Subjects in either Group 1 or Group 2 who enrolled in this substudy in ARC003 will be encouraged to continue participation in ARC004 but will need to be re-consented to do so. Subjects enrolled in both ARC004 and this substudy will undergo saliva collection coordinated at the designated ARC004 study visits. Otherwise these subjects will be treated according to the ARC004 study protocol.

Schedule of Events for the Exploratory Biochemical and Molecular Substudy

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

Abbreviations: GI = gastrointestinal; OIT = oral immunotherapy; wk = weeks

a Minimum study weeks are shown. Actual duration may be longer depending on subject's actual up-dosing in ARC004.

b For subjects who terminate dosing and enter observational follow-up, as per Section 7.3.3.2 of the ARC004 protocol. This sample is to be collected at the sixth monthly visit after study withdrawal or as close as practicable.

c Subjects withdrawing early from ARC004 with GI symptoms that were not already enrolled in this substudy may be approached to provide consent to enroll upon early termination.

Group 2 subjects (ie, subjects receiving active treatment with AR101 in ARC003) who were previously consented for this substudy in ARC003 and elect to continue in ARC004 will not provide additional specimens unless they develop symptoms during ARC004. Group 1

subjects in this substudy will undergo 3 protocol-specified collections of saliva. All Group 1 subjects will have a baseline saliva sample collected at Screening and baseline (before the first dose of AR101 in ARC004). Subjects who develop GI-predominant AEs that prompt their withdrawal from ARC004 or a protracted disruption of dosing with study product will be considered "cases" in this substudy. The second saliva sample will be collected from cases when the first PEESS v2.0 is completed. The final saliva sample for cases will be collected at the end of the protocol-defined 6-month follow-up period for subjects that withdraw from therapy.

"Controls" in this substudy will be defined as ARC004 participants receiving OIT who do not develop intolerable GI symptoms. Following the baseline collection, asymptomatic subjects will provide saliva samples at the 6-week up-dosing visit and again at the end of the Up-dosing period.

This substudy will principally involve: collection, shipment, and banking of saliva samples at specified time points; gene expression analysis of selected salivary biospecimens; and correlation with basic biometric data (eg, peripheral blood eosinophils, clinical symptom reports/PEESS v2.0 scores) obtained as necessary, and clinical outcome per the ARC004 protocol. Biochemical detection of eosinophil activation products or metabolites may also be possible from collected samples.

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

Case Definition: ARC004 Events Triggering PEESS v2.0

The following passage is adapted from Section 7.3.3.2 of the ARC004 Protocol, and serves to identify the case definition in this substudy; eg, the ARC004 subjects who develop the GI AEIs requiring further evaluation.

> *GI AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered AEIs and will be assessed longitudinally according to the procedures described below. For the purpose of delineating these AEIs, prolonged disruption of dosing is defined as withholding study product for > 7 days. This will include 3 categories of subjects:*
>
> - *Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (Section 7.3.3.2 of the ARC004 protocol)*
> - *Any subject who develops chronic/recurrent GI AEs at or before reaching the 20-mg dose level and resumes dosing after a 30-day dosing hiatus (Section 7.3.3.2 of the ARC004 protocol);*
> - *Any subject who permanently discontinues dosing who had experienced GI AEs (Section 7.3.3.2 of the ARC004 protocol).*

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

Exploratory Endpoints

All endpoints in this substudy are considered exploratory. The primary objective is to characterize RNA expression patterns in salivary specimens collected from peanut-allergic subjects who participated in a study of peanut OIT and developed intolerable GI AEs that interfered with treatment (ie, resulted in reducing, withholding, or discontinuing OIT dose levels). ARC004 subjects who do not develop dose-limiting GI symptoms will also be studied as control specimens. Secondarily we will also examine the associations of the salivary RNA expression changes with selected clinical variables and explore the within-subject correlation to RNA expression patterns observed in esophageal specimens, when available.

Bioinformatic Analysis Plan for Primary and Secondary Objectives

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

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

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

Criteria for Study Participation

Inclusion Criteria

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

- Participation in the ARC004 study
- Written informed consent from adult subjects
- Written informed consent from parent/guardian for minor subjects
- Written assent from minor subjects as appropriate (ie, above the age of 7 years)

Exclusion Criteria

Otherwise ineligible for ARC004

Subject Termination from the Substudy

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

Study Product

No study product will be administered in the substudy.

Study Procedures

The following procedures will be performed:

1. Enrollment and Permissions
   - Obtain subject/parental signatures on IRB-approved informed consent/assent form.
2. Sample Collection, Handling, and Analysis Procedures
   - Saliva is the principal biospecimen to be collected in this study with the aid of a commercially available kit designed expressly for salivary RNA research purposes. Specific details for saliva collection will be provided to sites in a manual of procedures.
   - The results of blood samples for complete blood count, already collected in ARC004, will also be included in analyses relating to the secondary objectives of this substudy.
   - Biospecimens may be temporarily stored at investigational sites to facilitate batch shipping and receiving. All biospecimens will be packaged and transported to the investigative laboratory in a manner compliant with all local, state, and federal laws

and regulations, as per standard operating procedures of the shipping and receiving facilities.

- Analyses will include 1 or more of the following:
  - Transcriptome analysis
  - EoE diagnostic panel comprising a 96-gene quantitative polymerase chain reaction (qPCR) array
  - Profiling of local cytokine expression
  - Targeted analysis of expression of previously identified specific candidate genes
  - Analysis of single nucleotide polymorphisms in previously identified specific candidate genes
  - Inflammatory pathway analysis (Ingenuity, Toppfun, or David)
  - qPCR analysis
  - Immunohistochemistry or other protein detection methods (eg ELISA, Western blot, etc.).
  - Mass spectrometry
  - Flow cytometry

Lead Investigative Laboratory

The lead investigative laboratory is the following:

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

1. Safety Monitoring

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

2. Statistical Considerations

This substudy is a pilot characterization of biochemical and biomolecular markers in relation to GI side effects arising during peanut OIT in ARC004 subjects. The analyses to be conducted in this substudy are all considered exploratory in nature. As such, descriptive statistical techniques will be utilized to characterize demographic and basic clinical variables, with standard assessments for normality and adjustments as necessary. Measures of correlation and longitudinal repeated measures will be assessed with appropriate techniques (eg, regression modeling) as necessary. Statistical testing for differences between treatment groups or time points may be assessed, but specific hypotheses are not pre-specified.

3. Study Endpoint Assessment

All endpoints in this study are considered exploratory and are defined in the Study Procedures section above.

4. Subject and Demographic Data

Baseline Characteristics, Demographics, and Safety Data

Baseline and demographic characteristics may be reported for each subject enrolled in the present study as they were obtained in ARC003 and ARC004. Baseline and demographic data could include age, race, sex, body weight, and height. Other analyses involving safety data may also be performed.

Use of Medications

There will be no medications used in this substudy. Data from concomitant medication use in ARC003 and ARC004 related to AEs may be analyzed as part of this substudy.

5. Sample Size Calculations

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

Appendix 7: Longitudinally Applicable Exclusion Criteria

Eligibility for ARC004 enrollment requires that the subject does NOT meet any of ARC003's longitudinal exclusion criteria. These exclusion criteria are listed below:

- History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension (as described Section 5.10)
- History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen
- History of eosinophilic esophagitis (EoE) or other eosinophilic gastrointestinal (GI) disease
- Current participation in any other interventional study other than ARC003
- Subject is in "build-up phase" of immunotherapy to another allergen (ie, has not reached maintenance dosing)
- Severe asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] Criteria Steps 5 or 6, as described in Appendix 2.
- Mild or moderate asthma (2007 NHLBI Criteria Steps 1-4), if uncontrolled or difficult to control as defined by any of the following:
  - Forced expiratory volume in 1 second (FEV_1) < 80% of predicted, or ratio of FEV_1 to forced vital capacity (FEV_1/FVC) < 75% of predicted, with or without controller medications (only for age 6 years or greater and able to do spirometry) or
  - Inhaled corticosteroid (ICS) dosing of > 500 µg daily fluticasone (or equivalent ICSs based on NHLBI dosing chart)
- History of steroid medication use (via intravenous [IV], intramuscular [IM], or oral administration) in any of the following manners:
  - history of daily oral steroid dosing for > 1 month during the past year *or*
  - 2 burst oral (IM or IV) steroid courses, defined as ≥ 1 mg/kg of prednisone or prednisone equivalent, in the past year ≥ 1 week in duration
- Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin prick test (SPT), or double-blind, placebo-controlled food challenge (DBPCFC)
- Lack of an available palatable vehicle food to which the subject is not allergic
- Use of any therapeutic antibody (eg omalizumab, mepolizumab, reslizumab, etc.), any investigational peanut immunotherapy other than AR101 (eg, oral, sublingual, epicutaneous), or any other immunomodulatory therapy excluding corticosteroids within the past 6 months (Section 5.10)
- Use of beta-blockers (oral), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium channel blockers (as described Section 5.10).
- Pregnancy or lactation
- Having the same place of residence as another subject in the study

- Participation in another clinical trial, other than ARC003, within 30 days or 5 half-lives of the investigational product, whichever is longer, prior to enrollment
- Developing dose limiting symptoms in reaction to the placebo part of ARC003 screening DBPCFC
- History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema
- Allergy to oat
- Hypersensitivity to epinephrine and any of the excipients in the product