Aimmune Therapeutics, Inc.

CLINICAL STUDY PROTOCOL

Protocol Title:	A Multicenter, Open-Label, Longer-Term Study of AR101 Characterized Oral Desensitization Immunotherapy in Subjects Who Participated in a Prior AR101 Study
Investigational Drug:	AR101, also known as Palforzia, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp in the United States, and defatted powder of *Arachis hypogaea* L., semen (peanuts) in the European Union
Protocol Number:	ARC008
IND Number:	15463
EudraCT Number:	2017-001334-26
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Boulevard, Suite 300 Brisbane, CA 94005 United States Phone number: +1 650 614 5220
Medical Monitors:	PPD
Original Protocol:	31 May 2017

Global Amendments	**Country/Region-Specific Amendments**	
1.0 – 19 Dec 2017	Country (United Kingdom):	0.1 – 23 Oct 2017
2.0 – 11 May 2018	Region (Europe):	0.2 – 31 Oct 2017
3.0 – 24 Jul 2018	Country (Ireland):	0.3 – 06 Nov 2017
4.0 – 01 Nov 2019	Country (Sweden):	0.4 – 13 Dec 2017
5.0 – 28 May 2020	Country (Germany):	3.1 – 28 Aug 2019
6.0 – 22 Dec 2020		

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

Principal Investigator Protocol Acknowledgment

Clinical Study Protocol ARC008	Global Amendment 6.0 Date: 22 Dec 2020
Sponsor: Aimmune Therapeutics, Inc.	
Title: A Multicenter, Open-Label, Longer-Term Study of AR101 Characterized Oral Desensitization Immunotherapy in Subjects Who Participated in a Prior AR101 Study	

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

_____

Principal Investigator (Print)

_____ _____

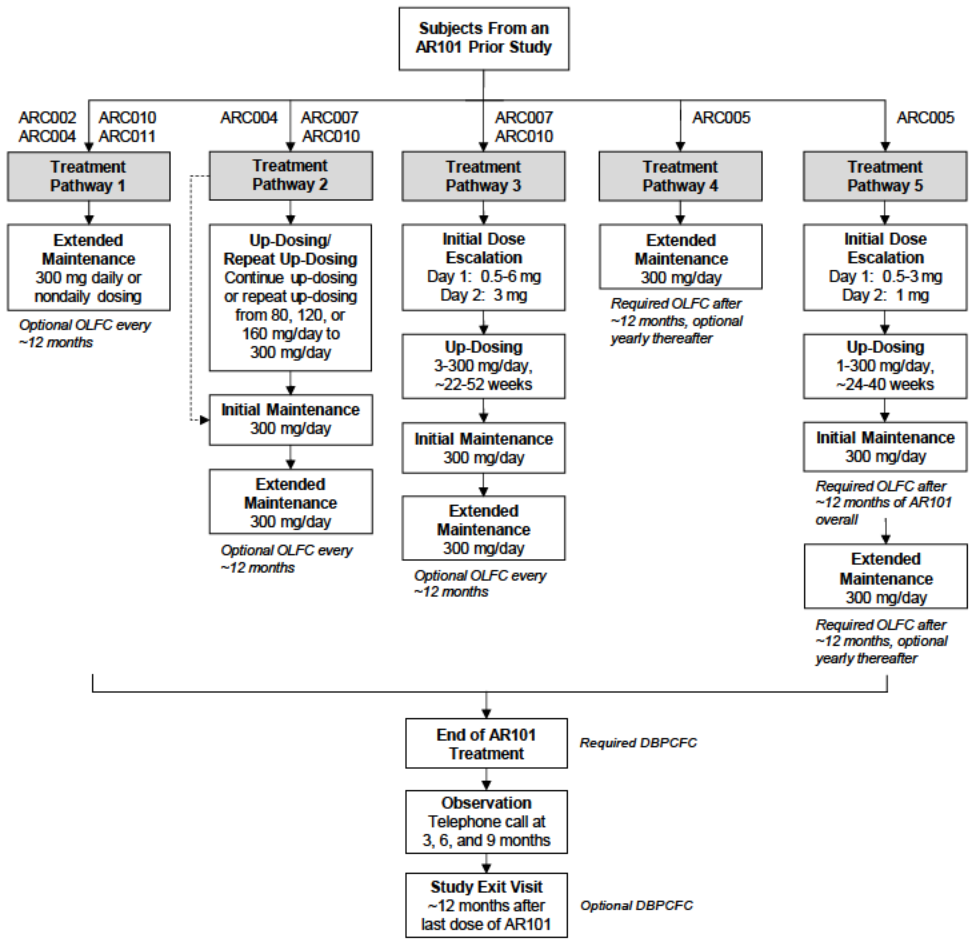
Principal Investigator (Signature) Date

Protocol ARC008 Synopsis		
Title	A Multicenter, Open-Label, Longer-Term Study of AR101 Characterized Oral Desensitization Immunotherapy in Subjects Who Participated in a Prior AR101 Study	
Short Title	Longer-Term Study of AR101 CODIT™	
Clinical Phase	3	
US IND	15463	
EudraCT	2017-001334-26	
Sponsor	Aimmune Therapeutics, Inc.	
Number of Subjects	The potential number of subjects who may be enrolled in this study is approximately 950.	
Purpose of Amendment 6.0	The main purpose of this amendment is to modify the study design to demonstrate a sustained clinical effect after 5 years total of AR101 treatment including all prior studies, and a 1-year observation period after stopping AR101 treatment.	
Objectives and Endpoints	**Objectives**	**Endpoints**
	Primary: To describe safety and tolerability during longer-term administration of AR101 and follow-up observation after the last dose of AR101	• Frequency of adverse events (AEs) • Frequency of premature discontinuation of AR101 dosing due to AEs • Frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs • Frequency of AEs that lead to a change in treatment regimen • Frequency of AEs that lead to early withdrawal • Frequency of anaphylaxis (as defined in Section 8.1.4.1) • Frequency of use of epinephrine as a rescue medication • Frequency of accidental/nonaccidental ingestion of peanut and other allergenic foods • Frequency of AEs following accidental/nonaccidental exposure to peanut and other allergenic foods • Frequency of eosinophilic esophagitis (EoE)
	Secondary: To assess the level of desensitization achievable through extended maintenance dosing of AR101	• Proportion of subjects tolerating each challenge dose in the open-label food challenge (OLFC) and the double-blind, placebo-controlled food challenge (DBPCFC) • The maximum tolerated challenge dose at each food challenge • Change in tolerated dose of peanut protein • Maximum severity of symptoms in each food challenge • Frequency of use of epinephrine as a rescue medication during the food challenges

	To characterize the interaction of AR101 and asthma control or nasal allergy symptoms in subjects with a history of asthma and/or allergic rhinitis	• Change in peak expiratory flow (PEF) • Change in Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) score • Change in Total Nasal Symptom Score (TNSS)
	To evaluate subjects' quality of life (QoL) and treatment satisfaction during AR101 treatment on daily and nondaily treatment regimens	• Changes in food allergy QoL scores as measured by Food Allergy Quality of Life Questionnaires (FAQLQ), and the Food Allergy Independent Measure (FAIM) questionnaire
	To evaluate parent/caregiver QoL during the child's treatment with AR101	• Change in Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire score
	Exploratory: To evaluate effects on immunologic parameters after longer-term administration of AR101 and follow-up observation after the last dose of AR101	• Change in peanut-specific and peanut component-specific serum immunoglobulin G subclass 4 (IgG4) • Change in total, peanut-specific, and peanut component-specific serum immunoglobulin E (IgE) • Change in peanut skin prick test (SPT) mean wheal diameter
	To evaluate changes in control of pre-existing asthma or atopic dermatitis in subjects from prior study ARC005	• Change in Test for Respiratory and Asthma Control in Kids (TRACK) and Eczema Area and Severity Index (EASI) scores
	This is an open-label, longer-term follow-on study of AR101 in subjects who participated in a previous AR101 clinical study. Descriptive statistics will be used to analyze the study data, and no formal hypothesis testing or sample size calculations are required. Therefore, the endpoints are not ordered in a statistical hierarchy.	
Study Design	**Treatment Pathways** ARC008 is a phase 3, international, open-label, longer-term study of an AR101 CODIT regimen in children and adults with peanut allergy. Subjects entering ARC008 will originate from an Aimmune AR101 clinical study or any future clinical study that identifies ARC008 as a potential poststudy option in the parent study protocol. Because the dosing regimens and procedures in the parent studies are not uniform, subjects will receive AR101 in 1 of 5 treatment pathways in ARC008: • **Treatment Pathway 1** is for subjects who received and tolerated AR101 in a daily or nondaily regimen in the parent study (except study ARC005). These subjects will have a Screening/Baseline visit, and eligible subjects will enter the Extended Maintenance Period. Subjects entering ARC008 on a dose > 300 mg once daily (QD) will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects from parent study ARC004 on nondaily regimens who did not tolerate 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects receiving nondaily AR101 regimens in parent study ARC004 who tolerated 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC will continue the nondaily AR101 regimen in the Extended Maintenance Period.	

	• **Treatment Pathway 2** is for the following subjects: – Subjects who did not complete their AR101 dosing regimen (eg, up-dosing, maintenance) in an eligible parent study (except study ARC005). – Subjects from parent study ARC004 or any future clinical study identifying ARC008 as its follow-on study, who received a nondaily AR101 dosing regimen and who did not tolerate this regimen. – Subjects from ARC004 who missed or withheld their nondaily AR101 dose for > 3 days, and subjects who received a nondaily AR101 dosing regimen and tolerated less than the 300 mg single dose of peanut protein (443 mg cumulative) at the ARC004 Exit DBPCFC, if continued treatment with AR101 was determined to be safe per investigator judgment and after discussion with the medical monitor. Subjects who did not complete their AR101 dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue the regimen in ARC008, proceeding through the applicable study periods until the End of Treatment visit. Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit, and eligible subjects will start the Repeat Up-Dosing Period at a dose of 80, 120, or 160 mg QD (a decrease in AR101 dose of approximately 50% to 75%) at the discretion of the investigator. These subjects will then proceed sequentially through the Initial Maintenance Period and Extended Maintenance Period. Subjects who complete the Repeat Up-Dosing Period or who tolerate AR101 300 mg QD for 2 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Initial Maintenance Period. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg QD for at least 24 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Extended Maintenance Period. In addition, ARC004 subjects who tolerated the nondaily regimen in ARC004 but who subsequently do not tolerate the nondaily regimen after entering ARC008 Treatment Pathway 1 may switch to Treatment Pathway 2 and start the Repeat Up-Dosing Period at investigator discretion. • **Treatment Pathway 3** is for subjects who received placebo in the parent study (except study ARC005). These subjects will undergo a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period with a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period. • **Treatment Pathway 4** is for subjects who received AR101 and tolerated the 300 mg/day dose for at least 2 consecutive weeks before the exit DBPCFC in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Extended Maintenance Period. • **Treatment Pathway 5** is for subjects who received placebo in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period at a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

Study Schematic



DBPCFC, double-blind, placebo-controlled food challenge; OLFC, open-label food challenge.

For subjects in Treatment Pathway 1, 2, or 4, initiation of AR101 in ARC008 occurs on the same day as or within 3 days after the Exit/Early Discontinuation visit in the parent study, unless specified otherwise in the parent study protocol. For subjects in Treatment Pathway 3 or 5, initiation of AR101 in ARC008 occurs on the same day as or within 10 days after the Screening/Baseline visit.

Treatment Pathway 2 only: Subjects who enter Treatment Pathway 2 in ARC008 soon after completing the ARC004 Early Discontinuation visit will enter the Repeat Up-Dosing Period after the Screening/Baseline visit. Subjects who complete the Repeat Up-Dosing Period or who tolerate AR101 300 mg/day for 2 weeks in ARC004 will proceed to the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg/day for at least 24 weeks in ARC004 will proceed to the Extended Maintenance Period after the ARC008 Screening/Baseline visit.

Study Visits and Periods

Screening/Baseline Visit (All Treatment Pathways)

Subjects treated with placebo in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment in ARC008, which should occur on the same day as or within 10 days after the Screening/Baseline visit.

Subjects treated with AR101 in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment in ARC008, which will occur on the same day as or within 3 days after the Exit visit or Early Discontinuation visit of the subject's parent study, unless specified otherwise in the parent study protocol.

	Initial Escalation Period (Treatment Pathways 3 and 5) All Initial Escalation Period doses will be administered by study site personnel under direct observation in the clinic. <u>Treatment Pathway 3</u> Eligible subjects will initiate AR101 at a dose of 0.5 mg of AR101 and then increase the dose incrementally at 20- to 30-minute intervals over the course of a single day to a maximum dose of 6 mg. Subjects who do not tolerate ≥ 3 mg dose on Day 1 will discontinue dosing and complete the End of Treatment visit. Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on the following day, Day 2. Subjects who tolerate this confirmatory dose will enter the Up-Dosing Period. Subjects who do not tolerate this confirmatory dose will discontinue dosing and complete the End of Treatment visit. <u>Treatment Pathway 5</u> Eligible subjects will begin initial dose escalation on Day 1 with a stepwise dose escalation of AR101 (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate the 3 mg dose on Day 1 will return on Day 2 for a single 1 mg dose. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin the Up-Dosing Period. Subjects who do not tolerate any dose on Day 1 or Day 2 will discontinue dosing and complete the End of Treatment visit. **Up-Dosing Period (Treatment Pathways 2, 3, and 5)** The Up-Dosing Period is designed to allow stepwise increases in AR101 dose over 2-week intervals to build up tolerance to the allergen while minimizing AEs. The first dose at each new dose level will be administered in the clinic. Subsequent doses will be dispensed to the subject or parent/caregiver and administered at home. To escalate to the next dose, a subject must be tolerating the current dose. Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt increasing the dose. <u>Treatment Pathway 2</u> Subjects who did not complete their AR101 up-dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue up-dosing in ARC008, proceeding through the applicable study periods until the End of Treatment visit. Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit in ARC008 and then enter a Repeat Up-Dosing Period, starting with a daily dose of AR101 at 80, 120, or 160 mg/day at the discretion of the investigator. The dose will be increased every 2 weeks until the maximum daily dose of 300 mg is reached. Subjects who tolerate the 300 mg/day dose for 2 weeks will receive 300 mg QD for 24 weeks in the Initial Maintenance Period. ARC004 subjects who tolerated the nondaily regimen in ARC004 but who subsequently do not tolerate the nondaily regimen after entering ARC008 Treatment Pathway 1 may switch to Treatment Pathway 2 and start the Repeat Up-Dosing Period at investigator discretion. <u>Treatment Pathway 3</u> Subjects in Treatment Pathway 3 will receive AR101 starting at a dose of 3 mg QD and escalate every 2 weeks to a maximum of 300 mg QD, according to the Up-Dosing Schedule. Those subjects who reach the target dose of 300 mg QD of AR101 will take this dose for 2 additional weeks as part of the Up-Dosing Period. Subjects who do not tolerate the 300 mg QD dose of AR101 for 2 weeks within 52 weeks (ie, must reach 300 mg dose by 50 weeks) after starting the Up-Dosing Period will discontinue dosing and complete the End of Treatment visit. Once a subject tolerates the 300 mg dose for

	2 weeks in the Up-Dosing Period, the subject will then enter the Initial Maintenance Period and receive the 300 mg dose for 24 weeks. Treatment Pathway 5 Subjects will receive AR101 starting at the 1 mg/day dose and dose escalation will occur every 2 weeks until the maximum daily dose of 300 mg is reached. Subjects who tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will begin the Initial Maintenance Period. Subjects who do not tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will discontinue dosing and complete the End of Treatment visit. **Initial Maintenance Period (Pathways 2, 3, and 5)** Subjects in Treatment Pathways 2, 3, and 5 who reach the target dose of 300 mg daily of AR101 and tolerate the dose for 2 additional weeks will return for an in-clinic visit to mark the End of Up-Dosing in this study. The following day, subjects will enter the Initial Maintenance Period and continue dosing with AR101 at 300 mg QD. Dosing on study visit days will take place in the clinic under direct observation. Subjects in Treatment Pathway 2 who completed the Up-Dosing/Repeat Up-Dosing Period or who tolerated AR101 300 mg QD for 2 weeks in ARC004 will enter the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who did not complete their AR101 maintenance regimen in an eligible parent study (except study ARC005) will have a Screening/Baseline visit and begin the Initial Maintenance Period in ARC008. Subjects in Treatment Pathways 2 and 3 will return for in-clinic visits at approximately Weeks 8 and 16 of the Initial Maintenance Period before returning at Week 24 to complete this Period and enter Extended Maintenance. Subjects in Treatment Pathway 5 will continue initial maintenance (with clinic visits every 4 weeks) for an overall total of approximately 12 months of treatment (including initial dose escalation, up-dosing, and maintenance treatment). The duration of initial maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the duration of up-dosing (24-40 weeks). Subjects in Treatment Pathway 5 will have an OLFC at the end of initial maintenance (ie, after an overall total of approximately 12 months of treatment). **Extended Maintenance Period (All Treatment Pathways)** The last treatment period for all treatment pathways is the Extended Maintenance Period. Subjects who completed initial maintenance in the parent AR101 study (Treatment Pathways 1 and 4) will enter the Extended Maintenance Period after the Screening/Baseline visit, and the other subjects (Treatment Pathways 2, 3, and 5) will enter this period after completing the Initial Maintenance Period in this study, after completing both the Repeat Up-Dosing and Initial Maintenance Periods in their parent study, or after receiving AR101 300 mg QD for at least 24 weeks in their parent study. During the Extended Maintenance Period, subjects will continue their current dosing regimen (300 mg QD, every other day [QOD], twice weekly [BIW], once weekly [QW], or every other week [QOW]), and study visits will occur approximately every 3 months. Subjects in Treatment Pathways 1, 2, and 3 who enter this period will have the option to participate in an OLFC to assess level of desensitization to peanut protein after 12 months in the Extended Maintenance Period and yearly thereafter. For subjects in Treatment Pathways 4 and 5, the OLFC after the first 12 months of extended maintenance treatment is required and then optional yearly thereafter. **End of Treatment Visit (All Treatment Pathways)** After protocol amendment 6.0 is approved at the study site: • Subjects in the United States (US) from prior studies ARC007 and ARC011 who have access to commercially available product will have the End of Treatment visit at their next scheduled study site (not remote) visit.

	• Subjects in the US from prior studies ARC002 or ARC004 who have access to commercially available product may have the End of Treatment visit at their next scheduled study site (not remote) visit if so directed by the study sponsor when necessary for operational considerations. • Subjects from prior study ARC005 will return to the study site for the End of Treatment visit when they complete at least approximately 3 years total of AR101 treatment including study ARC005 and AR101 is commercially available in their country, or discontinue early. • All other subjects will return to the study site for the End of Treatment visit when they complete at least approximately 5 years total of AR101 treatment including all prior studies and AR101 is commercially available in their country, or discontinue early. A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. All subjects will have telephone follow-up at least 14 days after the last dose of AR101 or last food challenge, whichever is last. **Follow-Up Observation Period (All Treatment Pathways)** The End of Treatment visit will be followed by a 12-month observation period. During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following: • Current treatment plan (eg, commercially available product, complete peanut avoidance, use of food equivalents for peanut oral immunotherapy, other investigational immunotherapy, other) • Events of systemic allergic reactions, EoE, accidental/nonaccidental exposures to food allergens and their outcomes, use of epinephrine, hospitalizations (all causes), emergency department visits (all causes), and serious adverse events **Study Exit Visit (All Treatment Pathways)** The Study Exit visit will be conducted approximately 12 months after the last dose of AR101. An optional DBPCFC may be performed.
Study Duration	The total duration of the study is approximately 10 years. The end of the study is defined as the last visit/assessment by the last subject in the study.
Study Discontinuation	Each subject will continue in the study until 1 or more of the following occurs: • The risk/benefit profile for the subject to continue in the study is no longer favorable in the opinion of the investigator. • The investigator withdraws the subject from the study. • The subject withdraws consent. • The sponsor discontinues development of AR101 in the relevant participating country. • Subject completes the End of Treatment visit and the 1-year follow-up observation period. After one of these events occurs, the subject will return to the clinic for the End of Treatment or Study Exit visit, as appropriate.
Investigational Product and Dispensing	AR101 will be provided in pull-apart capsules formulated to contain 0.5, 1, 10, 20, or 100 mg of peanut protein. Trained study site personnel will dispense the investigational product (IP) to the subject or the subject's parent/caregiver in a manner consistent with the assigned dose level. AR101 will also be provided as 300 mg of peanut protein supplied in foil-laminate sachets for use during the Initial Maintenance and Extended Maintenance Periods. AR101 should be kept refrigerated between 2°C and 8°C.

Inclusion Criteria	Subjects must meet all the following criteria to be eligible: 1. Prior participation in one of the following Aimmune AR101 clinical studies: ARC002, ARC004, ARC005, ARC007, ARC010, ARC011, or any future clinical study that identifies ARC008 as a follow-on study option in the protocol 2. Written informed consent from the subject or guardian/parent (or both parents where required by local authorities) in accordance with local institutional review board (IRB)/ethics committee (EC) guidelines 3. Written assent from the subject as required by local IRB/EC guidelines 4. Use of effective birth control by sexually active females of childbearing potential (Section 5.9.4)
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible: 1. Did not complete a minimum of 3 months of AR101 Maintenance in the parent study if subject was assigned to AR101 in that study, except for subjects in ARC004 who did not tolerate the nondaily AR101 dosing regimen, subjects in ARC007 or ARC010, or unless specified otherwise in the parent study 2. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of, becoming unstable or requiring a change in chronic therapeutic regimen, including malignancies occurring within 5 years prior to Screening and clinically active autoimmune diseases 3. Subjects with a history of alcohol, illicit or recreational drug or prescribed medication abuse 4. Developed a clinically significant change in health status during the parent study that, in the opinion of the investigator, would make the subject unsuitable for participation in this study 5. Taking a prohibited medication, as listed in Section 5.9.5, except during the follow-up observation period in this study 6. Currently participating in any other interventional clinical study other than the Aimmune parent study, except during the follow-up observation period in this study 7. Currently receiving or received within 5 years prior to Screening any type of peanut or other food allergen immunotherapy, except AR101 or unless allowed in the parent study, and except during the follow-up observation period in this study 8. Subject is living in the same household or is a dependent of sponsor employees and/or site staff involved in conducting this study, except for subjects originating from Aimmune Studies ARC002, ARC004, ARC007, ARC010, and ARC011 9. Currently in the build-up phase of immunotherapy for any non-food allergen, except during the follow-up observation period in this study 10. Hypersensitivity to epinephrine or hypersensitivity to any of the excipients in the IP 11. Pregnant or breastfeeding 12. Inability to withhold antihistamines for 5 half-lives prior to the initial day of escalation or visits at which an SPT or food challenge is conducted 13. Discontinued early from the parent study for any safety reason, except a subject from study ARC004 who has experienced a lack of tolerance for a nondaily dosing regimen, and subjects who discontinued early from an eligible parent study due to AEs (including chronic or recurrent GI AEs) who require continued safety follow-up only 14. Currently committed to an institution (eg, psychiatric institution, prison) by virtue of an order issued by judicial or administrative authorities 15. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety 16. Subjects unable to follow the protocol requirements

Study Procedures	The procedures conducted during the study visits include but are not limited to the following: • Informed consent & assent • Inclusion & exclusion criteria • Medical & allergy history • AE review • Concomitant medications • Food allergen exposure update • Diary log review (Treatment Pathways 4 and 5 only) • Dispensing/return of AR101 • Compliance check • Complete/abbreviated physical examination • Vital signs • PEF • Serum (Screening only)/urine pregnancy test for sexually active females of childbearing potential • SPT • Complete blood count • Total, peanut-specific, and peanut component-specific serum IgE • Peanut-specific and peanut component-specific serum IgG4 • Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0, for subjects who had GI AEs of interest) • ACT/C-ACT (for subjects with known asthma only) (before PEF assessment) • TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only) (Treatment Pathways 4 and 5 only) • EASI (for subjects with eczema or atopic dermatitis only) (Treatment Pathways 4 and 5 only) • TNSS questionnaire (for subjects with known allergic rhinitis only) (Treatment Pathways 1, 2, and 3 only) • FAQLQ and FAIM (except Treatment Pathway 4) • FAQL-PB (Treatment Pathways 3 and 5 only) • In-clinic dosing • OLFC • DBPCFC • Peanut allergy training • Home dosing instruction • Telephone follow-up
Statistical Considerations	There is no sample size calculation for this study. The sample size will be determined by the number of eligible subjects from each of the prior AR101 studies who participate in this study. Data will be summarized using descriptive statistics. No specific hypothesis testing or comparisons are planned for this study.

Guidance on Study Conduct During a Pandemic, Epidemic, or Other Emergency Not Related to the Study	In the event of a pandemic (eg, Coronavirus Disease 2019 [COVID-19] pandemic), epidemic, or other emergency not related to the study (eg, natural disaster, act of war or terrorism), restrictions may be issued at the country, state, regional, and/or local level that may affect study conduct, the scientific integrity of the study, or the safety and well-being of study participants and study site staff. When such restrictions and associated challenges (eg, site closures; travel restrictions; quarantines; pandemic- or epidemic-related illness in subjects, parents, caregivers, or study site personnel) prevent the conduct of study site visits (ie, onsite) or access to study product for an extended period, changes to certain study procedures will be implemented in accordance with regulatory requirements to ensure subject safety and continued treatment, care, and sponsor oversight as described in Appendix 12.

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CCI

List of Abbreviations

Abbreviation	Definition
ACT	Asthma Control Test
AE	Adverse event
AEI	Adverse event of interest
AR101	Characterized peanut allergen, the investigational product for study ARC008
BIW	Twice weekly
BP	Blood pressure
C-ACT	Childhood Asthma Control Test
CBC	Complete blood count
CFR	Code of Federal Regulations
CODIT™	Characterized oral desensitization immunotherapy
CoFAR	Consortium of Food Allergy Research
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EASI	Eczema Area and Severity Index
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
EoE	Eosinophilic esophagitis
FAIM	Food Allergy Independent Measure
FAQL-PB	Food Allergy Quality of Life – Parental Burden
FAQLQ	Food Allergy Quality of Life Questionnaires
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G subclass 4
IND	Investigational new drug
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
OLFC	Open-label food challenge
OIT	Oral immunotherapy
PEESS v2.0	Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0
PEF	Peak expiratory flow
PRACTALL	Practical Allergy
QD	Once daily
QOD	Every other day
QoL	Quality of life
QOW	Every other week
QW	Once weekly
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SPT	Skin prick test
TNSS	Total Nasal Symptom Score
TRACK	Test for Respiratory and Asthma Control in Kids
US	United States

1 BACKGROUND AND RATIONALE

1.1 Background

Updated background information is provided in the AR101 investigator brochure.

Peanut allergy is a potentially serious condition that disproportionately affects children and is associated with severe allergic reactions, including life-threatening anaphylaxis. The prevalence of peanut allergy, like other food allergies, has been rising in the Western world and is estimated to be approximately 2% in children in both the United States (US) and Europe (Gupta, 2018; Turner, 2017; Nwaru, 2014).

Aimmune Therapeutics, Inc., a Nestlé Health Science Company (Aimmune) developed AR101, also known as Palforzia, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp in the US, and defatted powder of *Arachis hypogaea* L., semen (peanuts) in the European Union (EU), using a characterized oral immunotherapy (OIT) desensitization approach for patients with peanut allergy. On 31 Jan 2020, the US Food and Drug Administration (FDA) approved AR101 (Palforzia) as a treatment for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be administered to patients aged 4 to 17 years during initial dose escalation, and these patients may continue its use during up-dosing and maintenance. On 17 Dec 2020, the European Commission approved Palforzia as a treatment for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Use of Palforzia may be continued in patients 18 years of age and older. Palforzia should always be used in conjunction with a peanut-avoidant diet.

Other than Palforzia, the current standard of care in management of peanut allergy is a peanut-avoidant diet, along with education of the subject and family in the acute management of an allergic reaction, including ready access to self-injectable epinephrine. The burden of avoidance and the constant fear of accidental exposure negatively affect the health-related quality of life (QoL) for subjects and their families (Primeau, 2000; Avery, 2003; Buchanan, 2007; Sicherer, 2010; Hofmann, 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, 2002; Altschul, 2001; Vierk, 2002). Accidental exposures are common, with up to 50% of food-allergic subjects having ≥ 1 allergic reaction over a 2-year period (Sicherer, 1998).

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

There is evidence that OIT induces a clinically meaningful level of desensitization in most subjects and may also induce favorable immunologic changes over time. 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 more than mild allergy symptoms. In conjunction with a peanut-avoidant diet, this state should be sufficient to desensitize a peanut-allergic individual from the adverse effects of an accidental exposure to peanuts or peanut-containing foods.

1.2 Clinical Studies of AR101

Updated results for AR101 clinical studies are provided in the AR101 investigator brochure. Brief descriptions of the study designs are provided in this section.

1.2.1 ARC001 and ARC002

ARC001 was a phase 2, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of OIT with AR101 in children and adults 4 to 26 years of age with peanut allergy conducted in the US. The study is complete. ARC001 consisted of a Screening Period with a Screening double-blind, placebo-controlled food challenge (DBPCFC), an Initial Escalation Period, an Up-Dosing Period to a target dose of 300 mg once daily (QD), a Maintenance Period (300 mg QD for 2 weeks), and an Exit DBPCFC. Subjects were randomized to either AR101 or placebo in a 1:1 ratio. The primary endpoint of ARC001 was the percentage of desensitization responders, defined as subjects tolerating 300 mg peanut protein (443 mg peanut protein cumulative) with no more than mild symptoms at the Exit DBPCFC. The intent-to-treat population comprised 55 subjects: 29 in the AR101 group and 26 in the placebo group.

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

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

ARC003 (PALISADE) was a phase 3, international, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 characterized oral desensitization immunotherapy (CODIT™) in children and adults 4 to 55 years of age with peanut allergy (PALISADE Group of Clinical Investigators, 2018). The study is complete. Subjects were randomized to either AR101 or placebo in a 3:1 ratio. The study consisted of a Screening Period with a Screening DBPCFC, an Initial Escalation Period, an Up-Dosing

Period to a target dose of 300 mg QD maintained for 2 weeks, a Maintenance Period (approximately 24 weeks), and an Exit DBPCFC. A total of 555 subjects were randomized.

ARC004 was a phase 3, open-label, international, follow-on study for subjects who completed ARC003. The study is complete. ARC004 was designed to evaluate the effect of extending the dosing interval from daily to every other day (QOD), twice weekly (BIW), once weekly (QW), and every other week (QOW). Subjects who received AR101 during ARC003 participated in 1 of 5 dosing regimens for approximately 28 to 84 weeks, including an Extended Maintenance Period of at least 28 weeks. Subjects who received placebo in ARC003 had initial escalation and up-dosing to a target dose level of 300 mg QD, and continued that dose daily for the 24-week Initial Maintenance Period before having a DBPCFC. Subjects who tolerated ≥ 443 mg peanut protein cumulative at this DBPCFC continued treatment in the Extended Maintenance Period. At the end of the Extended Maintenance Period, all subjects had an Exit DBPCFC. After the end of participation in ARC004, eligible subjects could enroll in ARC008.

1.2.3 ARC007 (RAMSES) and ARC011 (RAMSES Follow-On Study)

ARC007 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of the safety of AR101 CODIT in children ages 4 to 17 years of age with peanut allergy conducted in the US and Canada. The study is complete. A total of 506 subjects were randomly assigned 2:1 to AR101 or placebo. No food challenges were conducted during the study. Subjects who received AR101, completed the Initial Escalation and Up-Dosing Periods, and tolerated the target dose of 300 mg QD for 2 weeks were eligible to enroll in study ARC011 described below. Subjects who received placebo were eligible to enroll in ARC008 directly and undergo initial escalation and up-dosing to a target dose level of 300 mg QD. Subjects who did not complete their AR101 up-dosing regimen in ARC007 and did not discontinue early due to adverse events (AEs) could enroll in ARC008.

ARC011 was a phase 3, open-label, extension study for subjects previously enrolled and treated with AR101 in the ARC007 (RAMSES) study and who reached the target dose of 300 mg QD. The study is complete. Upon entry into ARC011, subjects continued this dose regimen for approximately 24 weeks to generate additional safety data. Subjects who completed this Initial Maintenance Period could enroll in ARC008.

1.2.4 ARC010 (ARTEMIS)

ARC010 was a phase 3, multicenter, double-blind, placebo-controlled study of the efficacy and safety of AR101 CODIT in subjects aged 4 to 17 years with peanut allergy conducted in Europe. The study is complete. A total of 175 subjects were randomly assigned 3:1 to AR101 or placebo. Subjects who reached the target dose of 300 mg QD and maintained this dose for the approximately 12-week Maintenance Period had a DBPCFC. Subjects who received AR101 and subjects who received placebo were offered the opportunity to enter ARC008.

1.2.5 ARC005 (POSEIDON)

ARC005 is an ongoing phase 3, international, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in children aged 1 to < 4 years with peanut allergy. Approximately 132 subjects aged 1 to < 4 years will be randomly assigned 2:1 to blinded treatment with AR101 or placebo. Subjects will have a screening DBPCFC, initial dose escalation of study product (up to 4 single doses of 0.5, 1, 1.5, and 3 mg on day 1 and a single 1 mg dose on day 2), up-dosing (from 1 mg/day up to 300 mg/day with dose escalation approximately every 2 weeks), and maintenance treatment (300 mg/day daily until the subject completes approximately 12 months of treatment overall [including initial dose escalation, up-dosing, and maintenance]). An exit DBPCFC will be performed after the end of maintenance treatment. After study exit, eligible subjects will have the option to enroll in ARC008.

1.3 Rationale for the Current Study

ARC008 is an open-label, international, longer-term extension study for eligible subjects who participated in prior or future Aimmune AR101 clinical studies. The rationale for conducting ARC008 is as follows:

- To allow subjects who received placebo in Aimmune-sponsored clinical studies with AR101 to receive AR101 drug product
- To allow subjects who received AR101 in Aimmune-sponsored clinical studies to continue treatment
- To assess safety and tolerability during longer-term administration of AR101 and follow-up observation after the last dose of AR101
- To explore whether the level of desensitization to peanut protein is maintained or continues to increase after longer-term administration of AR101 and follow-up observation after the last dose of AR101

1.4 Known and Potential Risks and Benefits to Subjects

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

1.4.1 Risks

The risks of this study include AEs associated with AR101 treatment, risks from the oral food challenges, and risks of decreased vigilance in avoidance of peanut-containing foods.

1.4.1.1 Adverse Events Associated With AR101 Treatment

The most frequently reported AEs associated with AR101 treatment are mild to moderate symptoms of allergic reactions, especially those associated with the gastrointestinal (GI) tract. More specifically, AR101 CODIT has caused allergic symptoms of sneezing,

rhinorrhea, urticaria, angioedema, flushing, eczema flare-ups, ocular, nasal, and/or oral throat pruritus, nausea, vomiting, abdominal discomfort, abdominal pain, cramping, cough, wheezing, and shortness of breath, in addition to anaphylaxis as defined by the criteria published by the National Institutes of Allergy and Infectious Disease-Food Allergy and Anaphylaxis Network workgroup (Sampson, 2006).

In this protocol, anaphylaxis refers to anaphylactic events or systemic allergic reactions of any severity. Anaphylaxis is a prespecified AE of interest (AEI) and an identified risk of AR101 treatment, especially when cofactors are present that can augment allergic reactivity, such as exercise or viral infection.

As of 31 Jul 2020, 16 of 1237 AR101-treated subjects (1.3%) overall in the entire clinical development program experienced a severe event of anaphylaxis in 4 studies. Fifteen events were triggered by AR101 and 1 by an accidental food allergen exposure. Two events were considered serious. All subjects recovered and none required prolonged hospital admission or required intensive support with antihypotensive medication or intubation. Eleven subjects continued study treatment and 5 discontinued from their study. Thirteen subjects had 1 or more potential cofactors (exercise was the most common, 8 subjects).

In addition to anaphylaxis (systemic allergic reactions of any severity), eosinophilic esophagitis (EoE) is also an AEI. As of 31 Jul 2020, 16 cases of EoE were identified in subjects treated with AR101 overall in the AR101 clinical development program. EoE severity was mild for 4 subjects, moderate for 10 subjects, and severe for 2 subjects. Twelve cases were considered related to study treatment. All cases were considered nonserious by the investigators. Symptoms resolved or improved during follow-up after discontinuation of AR101 for 12 subjects, 1 subject continued to have dysphagia and was under the care of a gastroenterologist, and follow-up information was not available for 3 subjects in the ongoing study ARC008. It is unclear how many of these cases were present prior to AR101 treatment and how many were exacerbated or caused by AR101.

Asthma is a risk factor for life-threatening or fatal anaphylaxis in patients with food allergy. Patients with severe or uncontrolled asthma are excluded from AR101 clinical studies. As of 31 Jul 2020, 2 subjects (0.2%) overall in the AR101 clinical program experienced serious events of asthma related to AR101 treatment. Both subjects had a history of asthma. A moderate event of asthma (attack) was reported in 1 subject in 2019 and a moderate event of asthma (exacerbation) was reported previously in 1 subject in 2016. Additional information is provided in the investigator brochure.

1.4.1.2 Risks of Oral Food Challenges

Oral food challenges may induce an allergic response. Allergic reactions to oral food challenges can be severe and even life-threatening. However, in general, 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 moderate reaction. If subjects have allergic reactions during the challenges, they may need oral, intramuscular, or intravenous (IV) medications. In ARC008, subjects will be monitored appropriately, and any reaction will be treated in accordance with the study center standard

of care. Trained personnel, including a physician, as well as medications and equipment per Practical Allergy (PRACTALL) recommendations and study site standard operating procedures will be immediately available to treat any reaction (Sampson, 2012).

1.4.1.3 Risks of Decreased Vigilance

There may be a risk that subjects may decrease their vigilance against accidental peanut ingestion during participation in the study because they believe they are protected from it. This phenomenon has been reported in previous studies, and subjects in the study and their parents/caregivers 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 a subject who participates in this study will benefit from AR101 treatment.

Treatment with AR101 in the intent-to-treat population of subjects aged 4 to 17 years in both phase 3 studies ARC003 and ARC010 resulted in statistically significant treatment effects over placebo for their primary and key secondary efficacy endpoints. In ARC003, the treatment difference in the proportion of subjects who tolerated a single highest dose of peanut protein with no more than mild symptoms at the exit DBPCFC (AR101-placebo) was 63.2% ($p < 0.0001$) for at least 600 mg and 47.8% ($p < 0.0001$) for at least 1000 mg. In ARC010, the treatment difference in the proportion of subjects who tolerated a single highest dose of 1000 mg peanut protein with no more than mild symptoms at the exit DBPCFC was 56.0% ($p < 0.0001$). These data demonstrate meaningful clinical improvement after AR101 maintenance periods of approximately 6 months in ARC003 and 3 months in ARC010. Tolerability of single doses of 600 and 1000 mg peanut protein provides approximately 4.8-fold and 8-fold margins over the median estimated real-world eliciting dose of 125 mg peanut protein (Deschildre, 2016). Favorable treatment effects of AR101 compared with placebo were also observed for key secondary endpoints of desensitization response at other challenge dose levels and maximum severity of symptoms during the DBPCFCs. The reduced severity of symptoms and reduced use of epinephrine during the exit DBPCFCs for AR101-treated subjects compared with placebo-treated subjects indicate that allergic reactions following unintended exposure are likely to be less severe in patients receiving AR101. AR101 was approved as Palforzia for marketing in the US by the FDA in January 2020 and for marketing in the EU by the European Commission in December 2020.

1.4.3 AR101 Benefits and Risks Assessment

In summary, AR101 produces a high rate of successful desensitization to a clinically meaningful level of peanut protein, providing treated individuals the potential benefit of mitigating allergic reactions, including anaphylaxis, after unintended exposure to peanut, which continues to justify the acceptable risk.

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

2 OBJECTIVES

This is an open-label, longer-term follow-on study of AR101 in subjects who participated in a previous AR101 clinical study. Descriptive statistics will be used to analyze the study data, and no formal hypothesis testing or sample size calculations are required. Therefore, the endpoints are not ordered in a statistical hierarchy. The objectives and endpoints for this study are summarized in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary: To describe safety and tolerability during longer-term administration of AR101 and follow-up observation after the last dose of AR101	• Frequency of AEs • Frequency of premature discontinuation of AR101 dosing due to AEs • Frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs • Frequency of AEs that lead to a change in treatment regimen • Frequency of AEs that lead to early withdrawal • Frequency of anaphylaxis (as defined in Section 8.1.4.1) • Frequency of use of epinephrine as a rescue medication • Frequency of accidental/nonaccidental ingestion of peanut and other allergenic foods • Frequency of AEs following accidental/nonaccidental exposure to peanut and other allergenic foods • Frequency of EoE
Secondary: To assess the level of desensitization achievable through extended maintenance dosing of AR101	• Proportion of subjects tolerating each challenge dose in the open-label food challenge (OLFC) and the DBPCFC • The maximum tolerated challenge dose at each food challenge • Change in tolerated dose of peanut protein • Maximum severity of symptoms in each food challenge • Frequency of use of epinephrine as a rescue medication during the food challenges
To characterize the interaction of AR101 and asthma control or nasal allergy symptoms in subjects with a history of asthma and/or allergic rhinitis	• Change in peak expiratory flow (PEF) • Change in Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) score • Change in Total Nasal Symptom Score (TNSS)
To evaluate subjects' QoL and treatment satisfaction during AR101 treatment on daily and nondaily treatment regimens	• Changes in food allergy QoL scores as measured by Food Allergy Quality of Life Questionnaires (FAQLQ), and the Food Allergy Independent Measure (FAIM) questionnaire
To evaluate parent/caregiver QoL during the child's treatment with AR101	• Change in Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire score

Objectives	Endpoints
Exploratory: To evaluate effects on immunologic parameters after longer-term administration of AR101 and follow-up observation after the last dose of AR101 To evaluate changes in control of pre-existing asthma or atopic dermatitis in subjects from prior study ARC005	• Change in peanut-specific and peanut component-specific serum immunoglobulin G subclass 4 (IgG4) • Change in total, peanut-specific, and peanut component-specific serum immunoglobulin E (IgE) • Change in peanut skin prick test (SPT) mean wheal diameter • Change in Test for Respiratory and Asthma Control in Kids (TRACK) and Eczema Area and Severity Index (EASI) scores

3 STUDY DESIGN

3.1 Treatment Pathways

ARC008 is a phase 3, international, open-label, longer-term study of an AR101 CODIT regimen in children and adults with peanut allergy. Subjects entering ARC008 will originate from an Aimmune AR101 clinical study or any future clinical study that identifies ARC008 as a potential poststudy option in the parent study protocol.

Because the dosing regimens and procedures in the parent studies are not uniform, subjects will receive AR101 in 1 of 5 treatment pathways in ARC008:

- Treatment Pathway 1 is for subjects who received and tolerated AR101 in a daily or nondaily regimen in the parent study (except study ARC005). These subjects will undergo a Screening/Baseline visit, and eligible subjects will enter the Extended Maintenance Period. Subjects entering ARC008 on a dose > 300 mg QD will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects from parent study ARC004 on nondaily regimens who did not tolerate 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects receiving nondaily AR101 regimens in parent study ARC004 who tolerated 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC will continue the nondaily AR101 regimen in the Extended Maintenance Period.
- Treatment Pathway 2 is for the following subjects:
  - Subjects who did not complete their AR101 dosing regimen (eg, up-dosing, maintenance) in an eligible parent study (except study ARC005).
  - Subjects from parent study ARC004, or any future clinical study identifying ARC008 as a follow-on study, who received a nondaily AR101 dosing regimen and who did not tolerate this regimen.
  - Subjects from ARC004 who missed or withheld their nondaily AR101 dose for > 3 days, and subjects who received a nondaily AR101 dosing regimen and tolerated less than the 300 mg single dose of peanut protein (443 mg cumulative) at the ARC004 Exit DBPCFC, if continued treatment with AR101 was

determined to be safe per investigator judgment and after discussion with the medical monitor.

Subjects who did not complete their AR101 dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue the regimen in ARC008, proceeding through the applicable study periods until the End of Treatment visit. Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit, and eligible subjects will start the Repeat Up-Dosing Period at a dose of 80, 120, or 160 mg QD (a decrease in AR101 dose of approximately 50% to 75%) at the discretion of the investigator. These subjects will then proceed sequentially through the Initial Maintenance Period and Extended Maintenance Period. Subjects who complete the Repeat Up-Dosing Period or who tolerate AR101 300 mg QD for 2 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Initial Maintenance Period. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg QD for at least 24 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Extended Maintenance Period. In addition, ARC004 subjects who tolerated the nondaily regimen in ARC004 but who subsequently do not tolerate the nondaily regimen after entering ARC008 Treatment Pathway 1 may switch to Treatment Pathway 2 and start the Repeat Up-Dosing Period at investigator discretion.

- Treatment Pathway 3 is for subjects who received placebo in the parent study (except study ARC005). These subjects will undergo a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period with a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.
- Treatment Pathway 4 is for subjects who received AR101 and tolerated the 300 mg/day dose for at least 2 consecutive weeks before the exit DBPCFC in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Extended Maintenance Period.
- Treatment Pathway 5 is for subjects who received placebo in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period at a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

3.1.1 Switching Treatment Pathways

Subjects who develop safety or tolerability concerns while on daily treatment with AR101 in any Treatment Pathway will have their dosing regimen adjusted per Section 6.8. It is possible that a subject who tolerated a nondaily regimen in the parent study will enter ARC008 on Treatment Pathway 1 but subsequently develop safety or tolerability concerns during Extended Maintenance. Such subjects, per investigator judgment, will switch from Treatment Pathway 1 to Treatment Pathway 2 to undergo Repeat Up-Dosing and continue maintenance dosing at 300 mg daily; alternatively, they can be discontinued from the study. Other situations may arise where the investigator decides that it is in the best interest of the

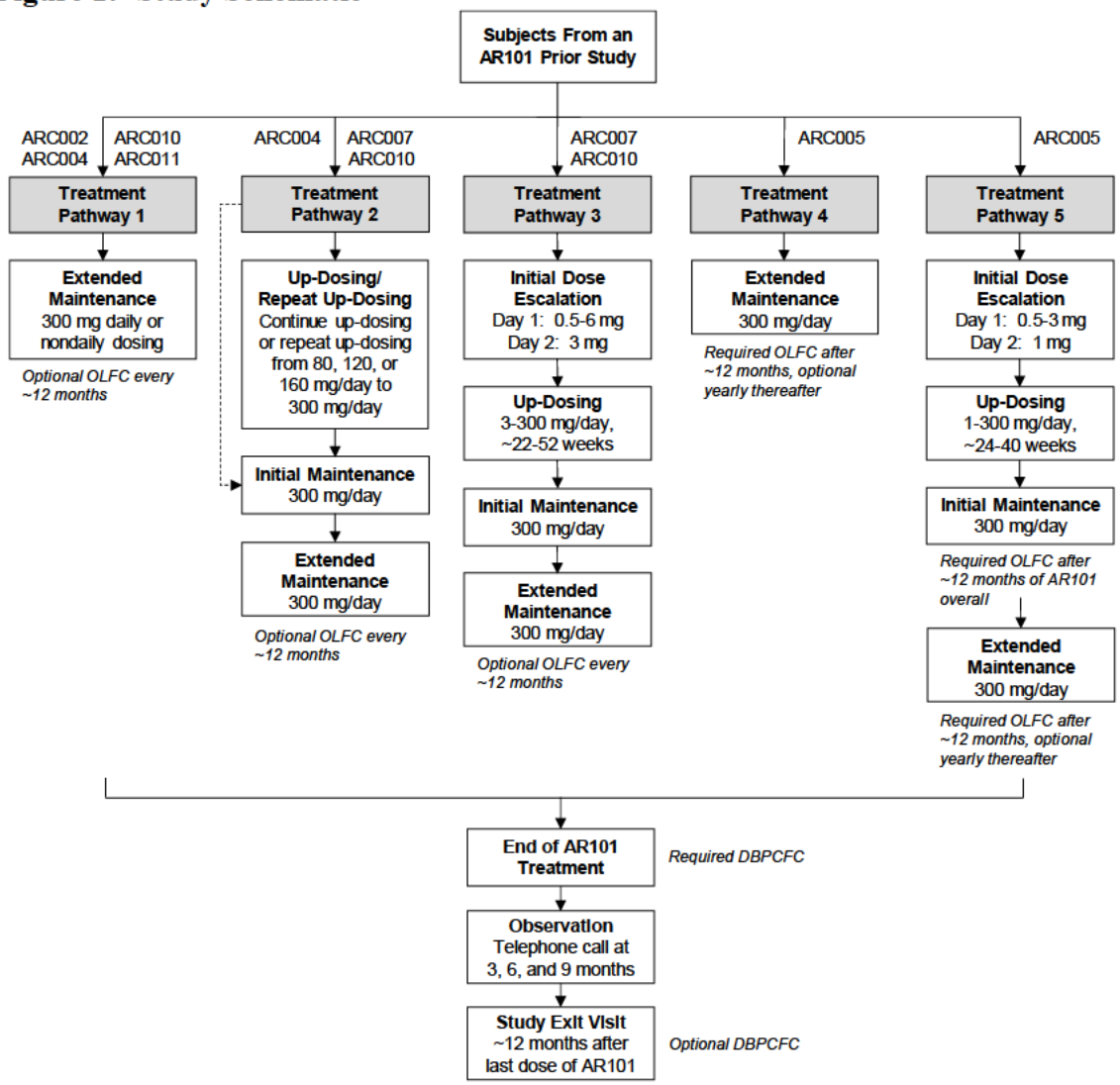
subject to switch to Treatment Pathway 2. All such cases must be discussed with the medical monitor who must agree prior to switching. The most likely scenarios are as follows:

- Simple nonadherence: Subjects who miss more than 2 consecutive scheduled nondaily doses (eg, QOD dosing regimen, subject misses Monday and Wednesday doses) during any part of the study other than for treatment of an AE or a dispensing error
- Medically necessary dose interruptions: Subjects who miss more than 4 consecutive scheduled nondaily doses due to medically indicated circumstances (eg, as part of the treatment for intercurrent AEs)
- Safety / tolerability concerns: Any subject on nondaily dosing having 1 related serious adverse event (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 transferred from Treatment Pathway 1 to Treatment Pathway 2 for safety reasons. Alternatively, they may be discontinued from ARC008.

3.2 Study Visits and Periods

The study schematic is shown in Figure 1 and the study visits and periods are briefly described in the sections that follow. The details of procedures to be performed at each visit are provided in Section 7 and the Schedules of Events in the appendices.

Figure 1: Study Schematic



DBPCFC, double-blind, placebo-controlled food challenge; OLFC, open-label food challenge.

For subjects in Treatment Pathway 1, 2, or 4, initiation of AR101 in ARC008 occurs on the same day as or within 3 days after the Exit/Early Discontinuation visit in the parent study, unless specified otherwise in the parent study protocol. For subjects in Treatment Pathway 3 or 5, initiation of AR101 in ARC008 occurs on the same day as or within 10 days after the Screening/Baseline visit.

Treatment Pathway 2 only: Subjects who enter Treatment Pathway 2 in ARC008 soon after completing the ARC004 Early Discontinuation visit will enter the Repeat Up-Dosing Period after the Screening/Baseline visit. Subjects who complete the Repeat Up-Dosing Period or who tolerate AR101 300 mg/day for 2 weeks in ARC004 will proceed to the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg/day for at least 24 weeks in ARC004 will proceed to the Extended Maintenance Period after the ARC008 Screening/Baseline visit.

In the event of a pandemic (eg, Coronavirus Disease 2019 [COVID-19] pandemic), epidemic, or other emergency not related to the study (eg, natural disaster, act of war or terrorism), restrictions may be issued at the country, state, regional, and/or local level that

may affect study conduct, the scientific integrity of the study, or the safety and well-being of study participants and study site staff. When such restrictions and associated challenges (eg, site closures; travel restrictions; quarantines; pandemic- or epidemic-related illness in subjects, parents, caregivers, or study site personnel) prevent the conduct of study site visits (ie, onsite) or access to study product for an extended period, changes to certain study procedures will be implemented in accordance with regulatory requirements to ensure subject safety and continued treatment, care, and sponsor oversight as described in Appendix 12.

3.2.1 Screening/Baseline Visit (All Treatment Pathways)

Subjects who received placebo in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment, which should occur on the same day as or within 10 days after the Screening/Baseline visit. Subjects who received AR101 in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment, which will occur on the same day as or within 3 days after the Exit visit or Early Discontinuation visit of the subject's parent study unless specified otherwise in the parent study protocol.

For the purposes of this study, there will be no day 0.

3.2.2 Initial Escalation Period (Treatment Pathways 3 and 5)

All Initial Escalation Period doses will be administered by study site personnel under direct observation in the clinic.

Initial dose escalation may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

Treatment Pathway 3

Eligible subjects will initiate AR101 at a dose of 0.5 mg of AR101 and then increase the dose incrementally at 20- to 30-minute intervals over the course of a single day to a maximum dose of 6 mg, according to the schedule in Table 2.

Table 2: Initial Escalation Schedule (Subjects Who Received Placebo in the Prior Study [Except ARC005])

Day 1 Dose Number	AR101 Dose, mg[a]	Cumulative AR101 Dose, mg[a]
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[a]**	**Cumulative AR101 Dose, mg[a]**
1	3	3

Note: Doses will be delivered at 20 to 30 minute intervals under direct observation.

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

Subjects who do not tolerate ≥ 3 mg dose on Day 1 will discontinue dosing and complete the End of Treatment visit.

Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on the following day, Day 2. Subjects who tolerate this confirmatory dose will enter the Up-Dosing Period. Subjects who do not tolerate this confirmatory dose will discontinue dosing and complete the End of Treatment visit.

Treatment Pathway 5

Eligible subjects will begin initial dose escalation on Day 1 with a stepwise dose escalation of AR101 (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated (Table 3).

Subjects who tolerate the 3 mg dose on Day 1 will return on Day 2 for a single 1 mg dose. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin the Up-Dosing Period. Subjects who do not tolerate any dose on Day 1 or Day 2 will discontinue dosing and complete the End of Treatment visit.

Table 3: Initial Escalation Schedule for Subjects Who Received Placebo in Study ARC005

Day 1 Dose Number	AR101 Dose (mg)	Cumulative Dose (mg)
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
Day 2 Dose Number	**AR101 Dose (mg)**	**Cumulative Dose (mg)**
1	1	1

3.2.3 Up-Dosing Period (Treatment Pathways 2, 3, and 5)

The Up-Dosing Period is designed to allow stepwise increases in AR101 dose over 2-week intervals to build up tolerance to the allergen while minimizing AEs. The first dose at each new dose level will be administered in the clinic. Subsequent doses will be dispensed to the subject or parent/caregiver and administered at home.

To escalate to the next dose, a subject must be tolerating the current dose. Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt increasing the dose.

The duration of up-dosing may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

3.2.3.1 Treatment Pathway 2

Subjects who did not complete their AR101 up-dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue up-dosing in ARC008, proceeding through the applicable study periods until the End of Treatment visit.

Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit in ARC008 and then enter a Repeat Up-Dosing Period, starting with a daily dose of AR101 at 80, 120, or 160 mg/day at the discretion of the investigator. The dose will be increased every 2 weeks per Table 4 until the maximum daily dose of 300 mg is reached. Subjects who tolerate the 300 mg/day dose for 2 weeks will receive 300 mg QD for 24 weeks in the Initial Maintenance Period. Some subjects who tolerated the nondaily regimen in ARC004 may enter ARC008 on Treatment Pathway 1 but subsequently need to switch to Treatment Pathway 2 if they do not tolerate their nondaily regimen in ARC008. Such subjects will progress through the Repeat Up-Dosing Period in Treatment Pathway 2 as described in this section.

To escalate to the next dose, a subject must be tolerating the current dose (Section 6.8.2). Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt increasing the dose.

Table 4: Repeat Up-Dosing Schedule (Treatment Pathway 2)

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.

3.2.3.2 Treatment Pathway 3

Subjects in Treatment Pathway 3, having just completed the Initial Escalation Period, will receive AR101 starting at a dose of 3 mg QD and escalate every 2 weeks to a maximum of 300 mg QD, according to the Up-Dosing Schedule (Table 5). The Up-Dosing Period can last from 22 to 52 weeks.

Those subjects who reach the target dose of 300 mg QD of AR101 will take this dose for 2 additional weeks as part of the Up-Dosing Period. Subjects who do not tolerate the 300 mg QD dose of AR101 for 2 weeks within 52 weeks (ie, must reach 300 mg dose within 50 weeks) after starting the Up-Dosing Period will discontinue dosing and complete the End of Treatment visit. Once a subject tolerates the 300 mg dose for 2 weeks in the Up-Dosing Period, the subject will then enter the Initial Maintenance Period and receive the 300 mg dose

for 24 weeks. To escalate to the next dose, a subject must be tolerating the current dose (Section 6.8.2). Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt increasing the dose.

Table 5: Up-Dosing Schedule (Treatment Pathway 3)

Dose Number	Investigational Product Dose, mg[a]	Interval (Weeks)	Percent Increase From Previous Dose
1	3	2	—
2	6	2	100
3	12	2	100
4	20	2	67
5	40	2	100
6	80	2	100
7	120	2	50
8	160	2	33
9	200	2	25
10	240	2	20
11	300	2	25

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

3.2.3.3 Treatment Pathway 5

After completing the Initial Escalation Period, subjects in Treatment Pathway 5 will receive AR101 starting at the 1 mg/day dose and dose escalation will occur every 2 weeks until the maximum daily dose of 300 mg is reached (Table 6). Subjects who tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will begin the Initial Maintenance Period. Subjects who do not tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will discontinue dosing and complete the End of Treatment visit.

Table 6: Up-Dosing Schedule (Treatment Pathway 5)

Dose Number	Investigational Product Dose, mg[a]	Interval (Weeks)	Percent Increase From Previous Dose
1	1	2	Not applicable
2	3	2	200
3	6	2	100
4	12	2	100
5	20	2	67
6	40	2	100
7	80	2	100
8	120	2	50
9	160	2	33
10	200	2	25
11	240	2	20
12	300	2	25

Up-dosing begins with the first 1 mg/day dose of study product at home.
[a] Milligrams of peanut protein.

3.2.4 Initial Maintenance Period (Pathways 2, 3, and 5)

Subjects in Treatment Pathways 2, 3, and 5 who reach the target dose of 300 mg daily of AR101 and tolerate the dose for 2 additional weeks will return for an in-clinic visit to mark the End of Up-Dosing in this study. The following day, subjects will enter the Initial Maintenance Period and continue dosing with AR101 at 300 mg QD. Dosing on study visit days will take place in the clinic under direct observation.

Subjects in Treatment Pathway 2 who completed the Up-Dosing/Repeat Up-Dosing Period or tolerated AR101 300 mg QD for 2 weeks in ARC004 will enter the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who did not complete their AR101 maintenance regimen in an eligible parent study (except study ARC005) will have a Screening/Baseline visit and begin the Initial Maintenance Period in ARC008.

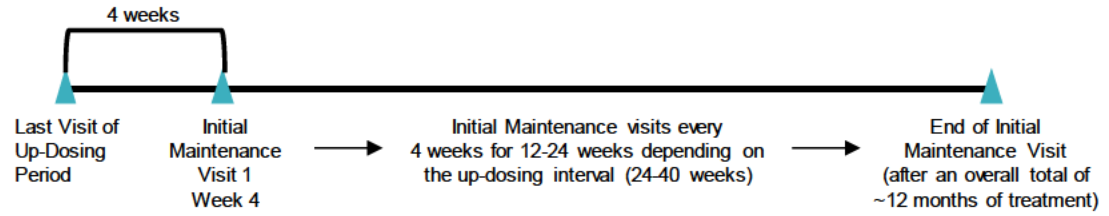
Subjects in Treatment Pathways 2 and 3 will return for in-clinic visits at approximately Weeks 8 and 16 of the Initial Maintenance Period before returning at Week 24 to complete this Period and enter Extended Maintenance (Figure 2).

Subjects in Treatment Pathway 5 will continue initial maintenance (with clinic visits every 4 weeks) for an overall total of approximately 12 months of treatment (including initial dose escalation, up-dosing, and maintenance treatment) (Figure 3). The duration of initial maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the duration of up-dosing (24-40 weeks). Subjects in Treatment Pathway 5 will have an OLFC at the end of initial maintenance (ie, after an overall total of approximately 12 months of treatment).

The duration of maintenance treatment may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

Figure 2: Initial Maintenance Period Visits (Treatment Pathways 2 and 3)

Figure 3: Initial Maintenance Period Visits (Treatment Pathway 5)



3.2.5 Extended Maintenance Period (All Treatment Pathways)

The last treatment period for all treatment pathways is the Extended Maintenance Period. Subjects who completed initial maintenance in the parent AR101 study (Treatment Pathways 1 and 4) will enter the Extended Maintenance Period after the Screening/Baseline visit, and the other subjects (Treatment Pathways 2, 3, and 5) will enter the Extended Maintenance Period after completing the Initial Maintenance Period in this study, after completing both the Repeat Up-Dosing and Initial Maintenance Periods in their parent study, or after receiving AR101 300 mg QD for at least 24 weeks in their parent study.

During the Extended Maintenance Period, subjects will continue their current dosing regimen (300 mg QD, BIW, QW, or QOW) so long as they continue to tolerate it. At any point during ARC008, subjects on nondaily dosing regimens may switch to Treatment Pathway 2 and enter Repeat Up-Dosing if they do not tolerate nondaily dosing.

For subjects continuing nondaily dosing, the dosing intervals should be as consistent as possible, preferably on the same day(s) each week.

- For BIW dosing regimen, doses should be at least 3 days apart (eg, Monday and Thursday each week)
- For QW dosing regimen, doses should be taken on the same day (±1 day) each week

- For QOW dosing regimen, doses should be taken on the same day (±2 days), every alternate week
- Study visits will occur approximately every 3 months until the study ends (Section 3.6).

Subjects in Treatment Pathways 1, 2, and 3 who enter this period will have the option to participate in an OLFC to assess level of desensitization to peanut protein after 12 months in the Extended Maintenance Period and yearly thereafter. For subjects in Treatment Pathways 4 and 5, the OLFC after the first 12 months of extended maintenance treatment is required and then optional yearly thereafter.

3.2.6 End of Treatment Visit (All Treatment Pathways)

After protocol amendment 6.0 is approved at the study site:

- Subjects in the US from prior studies ARC007 and ARC011 who have access to commercially available product will have the End of Treatment visit at their next scheduled study site (not remote) visit.
- Subjects in the US from prior studies ARC002 or ARC004 who have access to commercially available product may have the End of Treatment visit at their next scheduled study site (not remote) visit if so directed by the study sponsor when necessary for operational considerations.
- Subjects from prior study ARC005 will return to the study site for the End of Treatment visit when they complete at least approximately 3 years total of AR101 treatment including study ARC005 and AR101 is commercially available in their country, or discontinue early.
- All other subjects will return to the study site for the End of Treatment visit when they complete at least approximately 5 years total of AR101 treatment including all prior studies and AR101 is commercially available in their country, or discontinue early.

A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. All subjects will have telephone follow-up at least 14 days after the last dose of AR101 or last food challenge, whichever is last.

Subjects with unresolved AEs at early discontinuation or at the end of AR101 treatment, or who have GI AEIs, will have safety follow-up (Section 4.4.2, Section 8.1.4.2).

3.2.7 Follow-Up Observation Period (All Treatment Pathways)

The End of Treatment visit will be followed by a 12-month observation period. During observation, management of peanut allergy will be guided by the subject's physician.

Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan (eg, commercially available product, complete peanut avoidance, use of food equivalents for peanut oral immunotherapy, other investigational immunotherapy, other)
- Events of systemic allergic reactions, EoE, accidental/nonaccidental exposures to food allergens and their outcomes, use of epinephrine, hospitalizations (all causes), emergency department visits (all causes), and SAEs

3.2.8 Study Exit Visit (All Treatment Pathways)

The Study Exit visit will be conducted approximately 12 months after the last dose of AR101. An optional DBPCFC may be performed.

3.3 Safety Monitoring by the Internal Safety Risk Management Team

Although the safety of peanut OIT and AR101 are well established overall, an internal team (safety risk management team) will monitor safety for the study. The team will be led by a safety physician and consist of individuals with extensive multicenter clinical study experience in clinical immunology (specifically, food allergies) and biostatistics. The team will meet at least quarterly to review the safety data in accordance with the team charter.

3.4 Study Design Rationale

3.4.1 AR101 Dose Regimen and Study Periods

The dose regimen in this study is based on the dosing regimen successfully used in the phase 2 studies, ARC001 and ARC002. The ARC001 dosing regimen was based on the work of the Consortium of Food Allergy Research (CoFAR) and its investigators. The basic structure of the dose regimen consists of a 2-day initial escalation at very low doses, followed by an up-dosing phase of dose escalations with a single dose level escalation occurring every 2 weeks, and then an initial maintenance phase followed by an extended maintenance phase. This dosing regimen was well tolerated and effective in previous studies (Burks, 2012), and the 300 mg target dose was well tolerated and had clinically important activity in the AR101 phase 3 studies.

In addition, the dosing regimen to be used in this study in the Maintenance and Extended Maintenance Periods is a 300 mg dose to be administered at the dosing interval that the subject last tolerated in a previous Aimmune-sponsored clinical study.

A follow-up observation period after the last dose of AR101 is included to assess sustained clinical effect of AR101 treatment.

3.4.2 Desensitization Measurement Procedures

In addition to food challenges, this study will investigate potential surrogate immunologic tests to assess desensitization. Specifically, the utility of total, peanut-specific, and peanut component-specific IgE, and peanut-specific and peanut component-specific IgG4 will be explored as surrogate markers of peanut allergy or response to OIT.

To measure the level of desensitization to peanut protein, OLFCs will be conducted as follows:

- Treatment Pathways 1, 2, and 3: an optional OLFC will be conducted at annual intervals beginning after 12 months in the Extended Maintenance Period
- Treatment Pathway 4: an OLFC will be required after the first 12 months in the Extended Maintenance Period and optional at annual intervals thereafter
- Treatment Pathway 5: an OLFC will be required at the End of Initial Maintenance and after the first 12 months in the Extended Maintenance Period, and optional at annual intervals thereafter

A DBPCFC will be performed at the End of Treatment visit to assess desensitization after longer-term administration of AR101, and then an optional DBPCFC will be performed after approximately 1 year of follow-up observation to assess continued desensitization.

The highest single dose of the food challenges will be 2000 mg peanut protein. The inclusion of a 2000 mg dose is consistent with previously published literature (Varshney, 2011; Blumchen, 2010; Jones, 2009), and represents 1 dose level above the dose tested in DBPCFCs in the AR101 phase 2 study ARC002. In study ARC002, approximately 65% of subjects treated for only about 9 months (of which approximately 3 months was maintenance dosing) passed a 1000 mg single dose challenge (2043 mg cumulative dose) without dose-limiting symptoms and would have been offered another dose level if available. Therefore, the 2000 mg dose level will further characterize the level of desensitization reached with AR101 CODIT.

3.4.3 Other Assessments

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

3.5 Number of Sites and Subjects

Study sites that enrolled subjects in eligible prior AR101 studies will conduct this study. The potential number of subjects who may be enrolled in this study is approximately 950.

3.6 Study Duration

The total duration of the study is approximately 10 years.

The end of the study is defined as the last visit/assessment by the last subject in the study.

The total duration of the study and duration of study treatment for individual subjects may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

3.7 Study Discontinuation

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

- The risk/benefit profile for the subject to continue in the study is no longer favorable in the opinion of the investigator.
- The investigator withdraws the subject from the study.
- The subject withdraws consent.
- The sponsor discontinues development of AR101 in the relevant participating country.
- Subject completes the End of Treatment visit and the 1-year follow-up observation period.

After one of these events occurs, the subject will return to the clinic for an End of Treatment or Study Exit visit, as appropriate.

4 SELECTION AND EARLY DISCONTINUATION OF SUBJECTS

4.1 Inclusion Criteria

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

1. Prior participation in one of the following Aimmune AR101 clinical studies: ARC002, ARC004, ARC005, ARC007, ARC010, ARC011, or any future clinical study of that identifies ARC008 as a follow-on study option in the protocol
2. Written informed consent from the subject or guardian/parent (or both parents where required by local authorities) in accordance with local institutional review board (IRB)/ethics committee (EC) guidelines
3. Written assent from the subject as required by local IRB/EC guidelines
4. Use of effective birth control by sexually active females of childbearing potential (Section 5.9.4)

4.2 Exclusion Criteria

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

1. Did not complete a minimum of 3 months of AR101 Maintenance in the parent study if subject was assigned to AR101 in that study, except for subjects in ARC004 who did not tolerate the nondaily AR101 dosing regimen, subjects in ARC007 or ARC010, or unless specified otherwise in the parent study
2. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of, becoming unstable or requiring a change in chronic therapeutic regimen, including malignancies occurring within 5 years prior to Screening and clinically active autoimmune diseases
3. Subjects with a history of alcohol, illicit or recreational drug or prescribed medication abuse
4. Developed a clinically significant change in health status during the parent study that, in the opinion of the investigator, would make the subject unsuitable for participation in this study
5. Taking a prohibited medication, as listed in Section 5.9.5, except during the follow-up observation period in this study
6. Currently participating in any other interventional clinical study other than the Aimmune parent study, except during the follow-up observation period in this study
7. Currently receiving or received within 5 years prior to Screening any type of peanut or other food allergen immunotherapy, except AR101 or unless allowed in the parent study, and except during the follow-up observation period in this study
8. Subject is living in the same household or is a dependent of sponsor employee and/or site staff involved in conducting this study, except for subjects originating from Aimmune Studies ARC002, ARC004, ARC007, ARC010, and ARC011
9. Currently in the build-up phase of immunotherapy for any non-food allergen, except during the follow-up observation period in this study
10. Hypersensitivity to epinephrine or hypersensitivity to any of the excipients in the investigational product (IP)
11. Pregnant or breastfeeding
12. Inability to withhold antihistamines for 5 half-lives prior to the initial day of escalation or visits at which an SPT or food challenge is conducted
13. Discontinued early from the parent study for any safety reason, except a subject from study ARC004 who has experienced a lack of tolerance for a nondaily dosing regimen, and subjects who discontinued early from an eligible parent study due to AEs (including chronic or recurrent GI AEs) who require continued safety follow-up only
14. Currently committed to an institution (eg, psychiatric institution, prison) by virtue of an order issued by judicial or administrative authorities
15. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety
16. Subjects unable to follow the protocol requirements

4.3 Screen Failures

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

4.4 Early Discontinuation

A subject may discontinue dosing with AR101 anytime if the investigator determines that continuation in the study is detrimental to the subject. Following early discontinuation, subjects will return to the clinic to complete the End of Treatment visit.

Early discontinuation procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

4.4.1 Criteria for Early Discontinuation

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

1. Pregnancy
2. Life-threatening symptoms (CoFAR grade 4; Appendix 9), including, but not limited to anaphylaxis resulting in hypotension, neurologic compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
3. Severe allergic hypersensitivity symptoms (CoFAR grade 3; Appendix 9) that require intensive therapy (to be determined by the investigator but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) or those that are recurrent. Subjects who experience severe symptoms (eg, severe nausea, rhinorrhea, or pruritus) that are not life-threatening, not requiring intensive therapy, and not associated with any other features indicating a serious clinical condition, and who the investigator feels are suitable to continue with the study, will be discussed with the medical monitor and may continue the study under close supervision if both the investigator and the medical monitor deem it appropriately safe to do so
4. Dose-limiting symptoms that occur at or before the 3 mg single dose on Initial Escalation Day 1 (Treatment Pathways 3 and 5 only)
5. Dose-limiting symptoms that occur on Initial Escalation Day 2 (Treatment Pathways 3 and 5 only)
6. Nonadherence: For subjects on a daily dose regimen, missing > 7 consecutive dosing days on any 1 occasion or missing 3 consecutive dosing days on 3 or more occasions during Up-Dosing, other than for treatment of an AE or a dispensing error
7. Extended dosing interruptions: For subjects on a daily dose regimen, any circumstances, including medical indications that require missed AR101 dosing for ≥ 15 consecutive days, with the exception of the voluntary 30-day hiatus for GI AEs
8. On 1 episode, failure to accomplish up-dosing to 300 mg AR101 daily after 3 attempts (Treatment Pathways 2 and 3 only)
9. On 1 dose-reduction episode, failure to identify a tolerated dose of AR101 after 3 attempts at dose reduction

10. Administration of more than 2 doses of epinephrine for the treatment of any single AR101-related allergic reaction
11. Subject desires to receive commercially available product
12. The sponsor discontinues participation of subjects in the US from parent studies ARC002, ARC004, ARC007, and ARC011 who have access to commercially available product per protocol amendment 6.0

A subject who discontinues AR101 treatment early will return to the clinic for the End of Treatment visit. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

After protocol amendment 6.0 is approved at the study site, subjects in the US from parent studies ARC007 and ARC011 who have access to commercially available product will have the End of Treatment visit at their next scheduled study site (not remote) visit. Subjects in the US from prior studies ARC002 or ARC004 who have access to commercially available product may have the End of Treatment visit at their next scheduled study site (not remote) visit if so directed by the study sponsor when necessary for operational considerations.

4.4.2 Safety Follow-Up

A subject who discontinues AR101 treatment early or has ongoing AEs at the end of AR101 treatment will be followed up for safety for a minimum of 14 days after the last AR101 dose, 14 days after the last food challenge, or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is later. In addition, a subject who discontinues AR101 because of chronic or recurrent GI AEs will be followed up monthly for a minimum of 6 months or until resolution or stabilization of all GI AEs (Section 8.1.4.2), whichever is longer.

If the investigator becomes aware of an SAE with a suspected causal relationship to AR101 that occurs within 30 days after the last AR101 dose in a subject treated by him or her, the investigator shall, without undue delay, report to the sponsor. Additionally, subjects who discontinued early from an eligible parent study due to AEs (including chronic or recurrent GI AEs) may continue safety follow-up in ARC008 as needed.

The Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0) questionnaire (Franciosi, 2011) will be completed by subjects with GI AEIs as described in Section 8.1.4.2. Parents/caregivers will also complete the PEESS v2.0 as appropriate. Subjects who discontinue AR101 treatment early due to chronic/recurrent GI AEs will return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed up with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms resolved or are assessed as stabilized with optimal medical management, or the investigator considers them irreversible.

Additional instructions for the follow-up of these subjects are provided in Section 8.1.4.2.

Safety follow-up procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

4.4.3 Lost to Follow-Up

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

4.4.4 Subject Replacement

Since this is a rollover study of subjects who have participated in at least 1 prior study with AR101, no subject who discontinues AR101 treatment early will be replaced.

5 STUDY TREATMENT

5.1 Formulation, Packaging, and Labeling

AR101 is characterized peanut allergen in the form of peanut flour, formulated with a bulking agent (maize starch, microcrystalline cellulose, and other excipients to prevent clumping) and a flow agent in premeasured graduated doses. The capsules used in the Initial Escalation Period and Up-Dosing Period of this study currently include the following strengths: 0.5, 1, 10, 20, and 100 mg each of peanut protein. AR101 is characterized by high performance liquid chromatography and by specific enzyme-linked immunosorbent assay for key allergenic proteins to demonstrate stability and lot-to-lot consistency.

AR101 capsules will be provided in prepackaged dosing kits. For the escalation periods, each individual kit will contain 21 daily doses at a given dose level, enough to supply 2 weeks of dosing plus a 7-day overage to accommodate potential visit scheduling issues.

For Initial and Extended Maintenance Period dosing, a 300 mg AR101 dose will be provided in sealed, foil-laminate sachets (1 sachet/day). Sachets will be provided in kits containing 35 individual doses.

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

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

study drug for the duration of the study. Temperature excursions may be allowed with specific instructions from the sponsor and as described in the pharmacy manual.

Dispensation of study product may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

5.2 Preparation, Administration, and Dosing

All doses scheduled to be administered on clinic visit days will be taken at the clinic. Subjects should withhold their daily home AR101 dose on in-clinic dosing days but should take all other prescribed medications as scheduled. Doses will be administered in the clinic under the direct supervision of an appropriately qualified healthcare provider and the oversight of a physician. This dose, intended for in-clinic administration, will be removed from the dosing kit for the assigned dose level. Once a dose is removed from the dosing kit, the kit must be dispensed to the subject or held at the site for documented destruction or return to the sponsor's designee (as instructed); dosing kits once opened cannot be used for any other dosing interval or any other subject.

At each clinic visit in the Up-Dosing, Initial Maintenance, and Extended Maintenance Periods, the subject or parent/caregiver will receive a kit of capsules or sachets to be taken at home according to the current dose level. The subject or parent/caregiver will be instructed to store the dosing kit in the refrigerator at all times other than when it is removed to obtain the daily dose, and to bring all unused capsules/sachets back to the clinic at the next visit. For Treatment Pathways 4 and 5 only, the parent/caregiver will be instructed to record the capsules/sachets taken at home in a diary log.

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

Procedures for preparation and administration of doses given in the clinic or at home are the same. Dose preparation will be completed by the subject or by a supervising adult. For in-clinic dosing, dose preparation may be performed by clinic staff or by the subject or parent/caregiver 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 and then lightly tapped on each half of the capsule to ensure full delivery of contents. When using a sachet, the sachet is to be cut over the vehicle food and the entire contents emptied into the food. The sachet should then be gently squeezed and shaken to ensure full delivery of contents. The contents of the capsules/sachets will be mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other palatable, age-appropriate food.

Care must be taken not to inhale the powder as this could provoke worsening of asthma or induce an allergic reaction. AR101 may not be added to food heated above room temperature before consumption. The vehicle food must be one to which the subject is not allergic. The volume of the vehicle food should be such that the entire AR101 dose can be consumed in a few spoonfuls. The AR101 dose should be consumed as promptly after mixing as practicable. If not consumed within 4 hours of mixing into a vehicle, the AR101-vehicle food mixture must be discarded and a new dose mixed prior to consumption. If preparing a new dose is not feasible (eg, due to limited supply), the AR101-vehicle food mixture may be stored for up to 24 hours under conditions appropriate for the vehicle food in which the AR101 was mixed. If there is a delay of more than 24 hours in consumption, this AR101-vehicle food mixture must be discarded and the process restarted with a new AR101 dose. It is recommended that each dose of AR101 be taken at a consistent time (within a 4-hour period) each day that the dose is to be taken. An interval of ≥ 8 hours should pass between doses. Per investigator judgment, a home dose may be split into 2 portions for tolerability, as further discussed in Section 6.9.3.

The following precautions must be followed:

- Except for on days with in-clinic dosing, the daily home dose will be taken as part of a meal or heavy snack. The subject must have other food (besides the matrix vehicle) in the stomach before taking the dose.
- Dosing at the evening meal is recommended for children so the subject can be observed and supervised in the home setting by their parent(s)/caregiver(s) for several hours after dosing.
- Subjects are to avoid activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths within 3 hours after dosing).
- Dosing should also not occur within 2 hours of bedtime.
- If a subject has engaged in strenuous exercise before the planned dosing time, dosing must be delayed until any signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.
- For subjects aged 1 to < 4 years: In case of illness with or without fever, or symptoms such as wheezing, worsening asthma, vomiting, or diarrhea, the parent/caregiver is to withhold the dose of study product from the subject and notify the study site of the symptoms and for possible dose adjustments.

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

Directions for the administration and dispensation of study product may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

5.3 Postdose Monitoring at the Clinic

All subjects will be monitored for AEs including allergic reactions following dosing in the clinic. The time period for monitoring the subject is dependent on the severity of any symptoms that occur (Section 8.2.2.1) and the study period (Section 7).

The occurrence of any severe symptoms that include hypoxia, hypotension, change in mental status, grade 3 severe anaphylaxis (as defined in Appendix 8), or intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction anytime must be discussed with the medical monitor, and the subject must discontinue dosing in the study.

5.3.1 Screening/Baseline Visit (Treatment Pathways 1, 2, and 4)

Subjects who are administered AR101 at the Screening/Baseline visit must be observed for at least 90 minutes after dosing. Vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes after the dose and approximately every 30 minutes thereafter until the end of observation. The observation period may be extended as described in Section 5.3.2.1.

5.3.2 Initial Dose Escalation Days (Treatment Pathways 3 and 5)

5.3.2.1 Day 1

Vital signs will be measured and signs and symptoms of allergic reaction assessed at 15 minutes after each dose and just prior to administration of the next dose. Doses will be administered at 20- to 30-minute intervals, but if the dose interval is extended because of symptoms, vital sign measurement and allergic sign/symptom assessment will then occur at 30-minute intervals and for the duration of the postdose observation period. Each subject will be observed for at least 90 minutes after the last dose; vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes after the dose and approximately every 30 minutes thereafter until the end of observation.

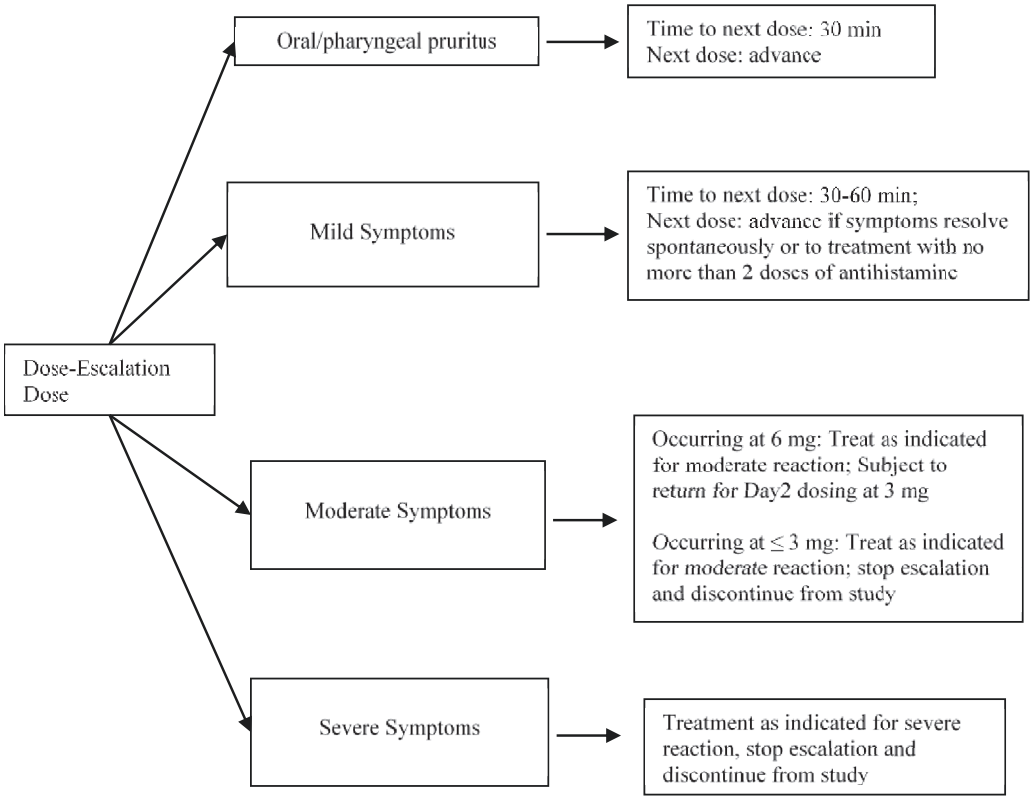
The postdose observation period will be conducted as follows:

- If dosing is completed with no symptoms detected before 90 minutes of observation after the last dose, the subject may be sent home from the clinic.
- If a subject exhibits **mild symptoms**, the observation period will be extended to a minimum of 1 hour after resolution of the symptoms. The subject may continue dosing in the study.
- If a subject experiences **moderate symptoms**, the observation period will be extended to a minimum of 2 hours after resolution of the symptoms. The subject will discontinue dosing in the study.
- If a subject experiences **severe symptoms**, the observation period will be extended to a minimum of 3 hours after resolution of the symptoms and will occur either at the

clinic or at an emergency facility, as appropriate. The subject will discontinue dosing in the study.

The actions to be taken for allergic symptoms that occur during Escalation Day 1 are shown in Figure 4.

Figure 4: Schematic for Initial Escalation Day 1



5.3.2.2 Day 2

Subjects must be observed for at least 90 minutes after dosing. Vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes after the dose and approximately every 30 minutes thereafter until the end of observation. The observation period will be extended as necessary as described in Section 5.3.2.1.

5.3.3 Up-Dosing Period (Treatment Pathways 2, 3, and 5)

Subjects must be observed for at least 90 minutes after dosing. Vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes after the dose and approximately every 30 minutes thereafter until the end of observation. The observation period will be extended as necessary as described in Section 5.3.2.1.

5.3.4 Initial Maintenance Period (Treatment Pathways 2, 3, and 5) and Extended Maintenance Period (All Treatment Pathways)

Subjects in Treatment Pathways 1, 2, and 3 must be observed for at least 30 minutes after dosing with vital sign measurements and assessment for signs and symptoms of allergic reaction. Postdose vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes postdose, and at 15- to 30-minute intervals thereafter if the postdose observation period is prolonged beyond the requisite 30 minutes.

Subjects in Treatment Pathways 4 and 5 must be observed for at least 90 minutes after dosing. Vital signs will be measured and signs and symptoms of allergic reaction assessed 15 to 30 minutes postdose, and approximately every 30 minutes thereafter until the end of observation. The postdose observation period during maintenance treatment may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.

The procedure for monitoring subjects for safety after in-clinic dosing is the same as for other visits (Section 5.3.2.1), except that the initial period of required postdose observation may be shortened to 30 minutes for tolerated doses.

5.4 Dosing After Missed, Withheld, or Delayed Doses

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

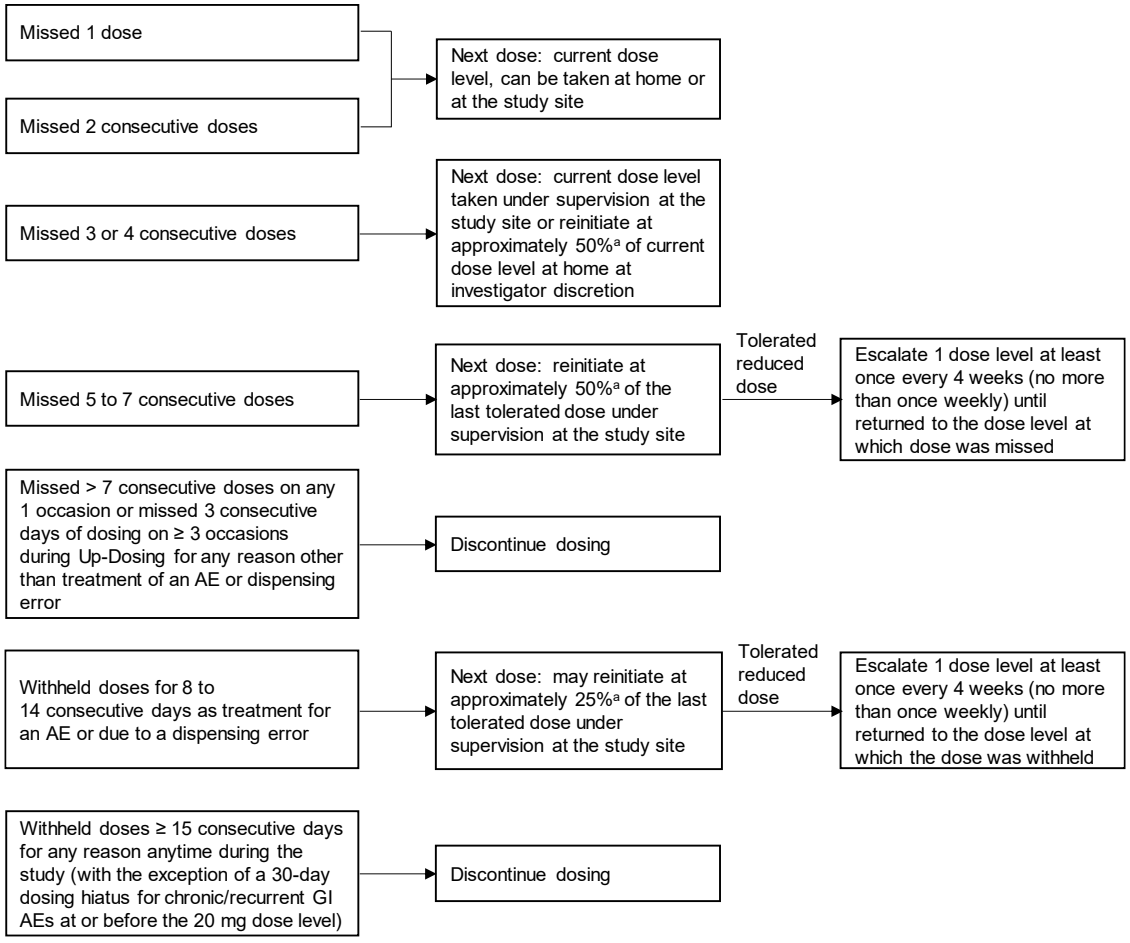
Missed doses of study product can pose a significant risk to subjects anytime during the study, and the greatest risk is considered to be during up-dosing. Missing 1 dose or 2 consecutive doses due to medical reasons (eg, intercurrent illness, AE) or for nonmedical reasons (eg, forgetting, intentional) cannot be avoided at times and is allowed. Missing 3 or more consecutive doses for medical reasons with investigator awareness is allowed and requires reinitiation of dosing under medical supervision. Missed doses for nonmedical reasons are allowed if the total number of missed doses between study visits is not excessive (ie, > 80% of dispensed doses were taken between study visits). Procedures and allowance for missed consecutive doses of study product during up-dosing and maintenance are described in the following sections.

5.4.1 Up-Dosing Period (Treatment Pathways 2, 3, and 5)

The dosing procedures to be followed after missed or withheld doses during the Up-Dosing Period are shown in Figure 5.

Procedures for missed consecutive doses may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

Figure 5: Dosing Procedures After Missed Consecutive Doses During the Up-Dosing Period



[a] Rounded to the nearest feasible whole dose or lower at investigator discretion.

AE, adverse event; GI, gastrointestinal.

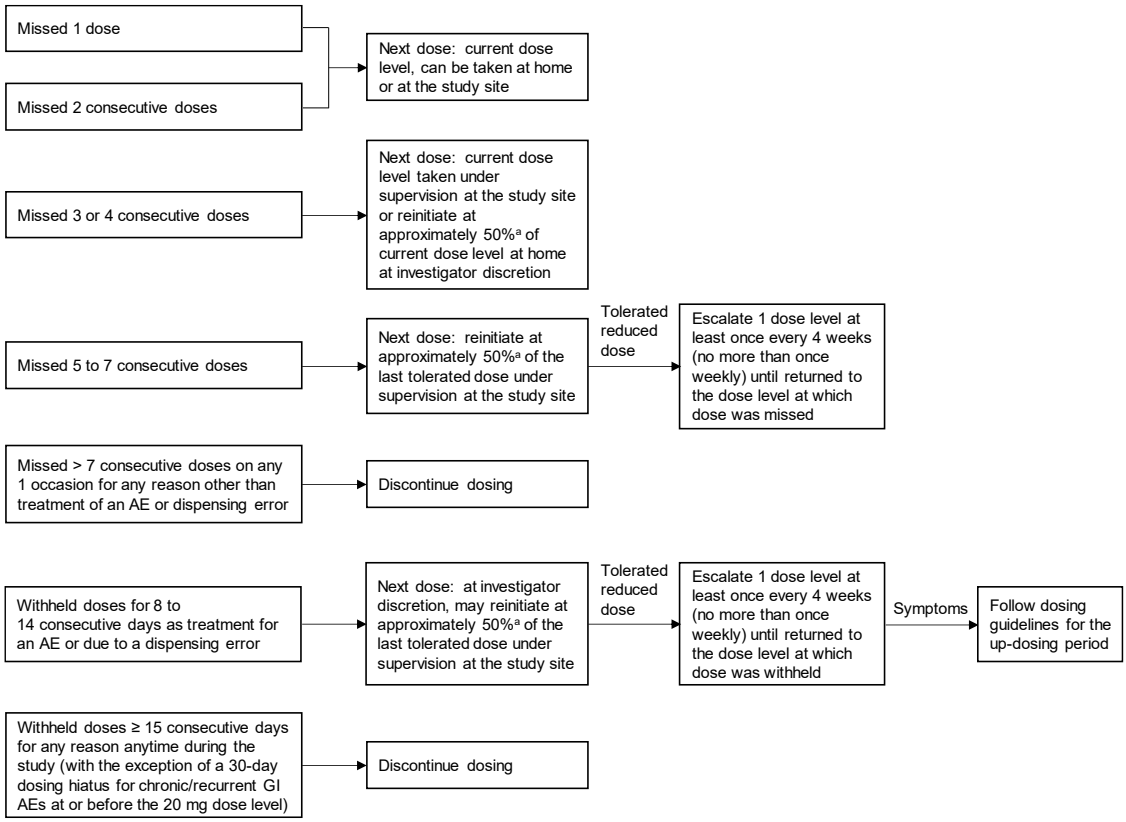
5.4.2 Initial Maintenance Period (Treatment Pathways 2, 3, and 5) and Extended Maintenance Period (All Treatment Pathways)

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

For subjects on daily regimens in the Initial Maintenance Period or Extended Maintenance Period, the dosing procedures to be followed after missed or withheld doses are shown in Figure 6.

Procedures for missed consecutive doses may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

Figure 6: Dosing Procedures After Missed Consecutive Doses During the Initial Maintenance or Extended Maintenance Period for Subjects on a Daily Dosing Regimen



[a] Rounded to the nearest feasible whole dose or lower at investigator discretion.
AE, adverse event; GI, gastrointestinal.

For subjects on nondaily regimens, a missed dose should be administered on the following day at approximately the same time of day as previously administered. Thereafter, the subject should return to the original schedule.

If on a nondaily regimen and a dose is missed or intentionally held for > 3 days past the time the dose was due to be taken, the investigator must discuss the case with a medical monitor prior to administering the next dose.

5.5 Modification of Study Treatment

AR101 doses may be adjusted by the investigator if the subject is unable to tolerate the scheduled dose level. If such a dose modification occurs, the subject will return all unused capsules/sachets of AR101 during a dose adjustment visit and be dispensed new capsules/sachets at the adjusted dose level. Specific dose adjustment procedures are discussed further in Section 6.8.3 and Section 6.9.

Dose adjustment procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

5.6 Drug Accountability

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

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

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

5.7 Assessment of Compliance With Study Treatment and Monitoring

Study site staff will contact the subject or parent/caregiver by telephone to enquire about AEs and about compliance with study product dosing according to the Schedules of Events in the appendices. Additionally, for Treatment Pathways 4 and 5 only, the subject's parent/caregiver will record daily dosing and any reaction to at home dosing and AEs occurring between clinic visits in the diary log. AR101 doses lost or destroyed at home will also be recorded in the diary log.

All used and unused AR101 wallets and sachet containers should be returned to the clinic at each visit.

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

Treatment compliance procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

5.8 Treatment of Overdose

Any dose of AR101 greater than the prescribed dose within 1 calendar day will be considered an overdose.

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

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

- Contact a medical monitor as soon as possible
- Closely monitor the participant for any AE and report as appropriate (Section 8.2).

- Record the quantity of the excess dose as well as the duration of the overdose in the source document
- Report the protocol deviation (Section 13).

5.9 Concomitant Medications

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

5.9.1 Prophylactic Medications

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

5.9.2 Rescue Medications

Treatment for individual acute allergic reactions during ARC008 should be according to recognized standards of care for allergy practice. In general, this could include either an antihistamine or epinephrine, along with IV fluids, a beta-adrenergic agonist (eg, albuterol), oxygen, or steroids, as indicated. Specific guidance about pharmacological and supportive treatments related to dosing reactions is provided in Section 6.9.

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

5.9.3 Symptomatic Treatment for Chronic and/or Recurrent Adverse Events

Symptomatic treatment for chronic/recurrent AEs is permitted (except for prohibited medications [Section 5.9.5]) but should be used to supplement dose reduction, not substitute for it. It is advised that an attempt to withdraw symptomatic therapy be made prior to dose re-escalation. If unsuccessful, symptomatic therapy may be resumed and dose escalation may proceed with the symptomatic therapy in place.

5.9.4 Contraception

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

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

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

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

- A highly effective method of birth control, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, as follows:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence
- If a highly effective single method of birth control is not used, an effective, double-barrier method of contraception should be used (eg, male condom in conjunction with a cervical cap, diaphragm, or contraceptive sponge with spermicide)

Where local requirements are more stringent, a highly effective method of birth control must be used.

5.9.5 Prohibited Medications

Use of the following medications is prohibited during the study, except during the follow-up observation period:

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

During the study, subjects may be at increased risk for anaphylaxis, which in severe form can result in a drop in 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 study. The use of medication with known cardiovascular side effects during the study is discouraged; however, if an investigator deems such use necessary, it must be undertaken with caution. It is beyond the scope of this protocol to list all drugs with cardiovascular side effects. Classes of drugs with a high potential for cardiovascular side effects include antipsychotics, cyclooxygenase-2 inhibitors (chronic use), nonsteroidal anti-inflammatory drugs (chronic use), antiarrhythmics, antihypertensives, and antineoplastics. Before a drug with cardiovascular side effects is used in conjunction with OIT, the investigator should discuss its use with a medical monitor.

It is beyond the scope of this protocol to list all immunomodulatory drugs; broadly, these include drugs to treat or prevent transplant rejection, autoimmune disease, and certain neoplasias (eg, cyclosporine, tacrolimus, antitumor necrosis alpha drugs, and other anti-cytokine drugs), as well as other allergen immunotherapies. If an investigator contemplates the use of a potentially immunomodulatory drug during the study, the investigator should discuss this with a medical monitor.

6 STUDY PROCEDURES

Study procedures including safety assessments are summarized in the following subsections.

Study procedures including safety assessments may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

6.1 Safety Assessments

6.1.1 Medical History/Allergy History

A complete medical and allergy history will be recorded in the source document at the Screening/Baseline visit.

6.1.2 Adverse Events

Assessments of AEs are presented in Section 8.

6.1.3 Concomitant Medications

Concomitant medications will be reviewed with the subject or parent/caregiver at each on-site visit as indicated in the Schedules of Events in the appendices, recorded in the source document, and updated at each visit.

6.1.4 Food Allergen Exposure Update

Food allergen exposure will be reviewed with the subject or parent/caregiver at each on-site visit as indicated in the Schedules of Events in the appendices, and recorded in the source document, and updated at each visit.

6.1.5 Physical Examination

Complete and abbreviated (symptom-directed) physical examinations will be conducted at the visits indicated in the Schedules of Events in the appendices and the findings recorded in the source document.

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

6.1.6 Vital Signs

Vital signs (BP, pulse rate, and body temperature) will be measured at the visits indicated in the Schedules of Events in the appendices and the measurements recorded in the source document. For Treatment Pathways 4 and 5, vital signs also include respiratory rate and oxygen saturation level. Measurement of BP and pulse rate should be preceded by at least 5 minutes of rest for the subject.

Reference ranges for BP, pulse rate, temperature, and respiratory rate in subjects aged 1 to 4 years are provided in Table 7. Investigators are to use the age-specific reference ranges for vital signs to determine whether the vital sign is abnormal and clinically significant.

Table 7: Reference Ranges for Vital Signs in Subjects Aged 1 to 4 Years

Vital Sign	Age (inclusive)	Lower Limit	Upper Limit	Units
Blood pressure [1]				
Diastolic	1-2 years	45	70	mm Hg
Diastolic	3-4 years	50	80	mm Hg
Systolic	1-2 years	75	105	mm Hg
Systolic	3-4 years	80	110	mm Hg
Pulse rate	1-2 years	80	130	Beats/minute
	3-4 years	80	120	Beats/minute
Temperature	All ages	36.6	37.3	Degrees Celsius
	All ages	97.8	99.1	Degrees Fahrenheit
Respiratory rate	1-2 years	20	35	Breaths/minute
	3-4 years	20	30	Breaths/minute

Source: Aimmune medical review of Drutz, 2019; Hughes, 2018 (table following Preface p.xii); Mersch, 2018.

[1] Per Sampson, 2006, reduced blood pressure after exposure to a known allergen for the subject (minutes to hours) is as follows:

- Infants and children: > 30% decrease from baseline in systolic blood pressure or low systolic blood pressure in children defined as follows:
  - Aged 1 month to 1 year: < 70 mm Hg
  - Aged > 1 to 10 years: < (70 mm Hg + [2 × age])

6.1.7 Complete Blood Count

Blood samples will be collected at the visits identified in the Schedules of Events in the appendices after the predose vital signs and PEF and before administration of AR101.

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

6.1.8 Pregnancy Test

All sexually active females of childbearing potential will undergo a serum pregnancy test at Screening and urine pregnancy testing at the visits indicated in the Schedules of Events (Appendix 1, Appendix 2, Appendix 3) and the results recorded in the source document.

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

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.

6.1.9 Pediatric Eosinophilic Esophagitis Symptom Scores Version 2.0

The PEESS v2.0 questionnaire (Franciosi, 2011) will be completed by subjects with GI AEIs as described in Section 8.1.4.2. Parents/caregivers will also complete the PEESS v2.0 as appropriate. Subjects who discontinue AR101 treatment early due to chronic/recurrent GI AEs will return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed up with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms are resolved or stable with optimal medical management or the investigator considers them irreversible, in which case the sponsor must be notified.

6.2 Desensitization Measurement Procedures

Desensitization measurement procedures will be conducted at the visits indicated in the Schedules of Events in the appendices and recorded in the source document.

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

6.2.1 Skin Prick Test

SPTs will be conducted at the visits indicated in the Schedules of Events in the appendices and wheal measurements recorded in the source document. SPTs will be performed using procedures for food allergens approved by both study site and the sponsor. At the time that the SPT is performed, the subject must have taken no antihistamines or other medications that could interfere with the assessment of the SPT for an appropriate length of time (eg, 5 half-lives of the antihistamine that is being used or other medications in question).

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

6.2.2 Open-Label Food Challenge

Subjects in Treatment Pathway 5 will have an OLFC at the end of initial maintenance (ie, after an overall total of approximately 12 months of treatment, including initial escalation, up-dosing, and maintenance). The OLFC is adapted for young children based on accepted food challenge procedures. During the OLFC at the end of initial maintenance, single doses of peanut protein (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) will be

conditionally tested using a food challenge mixture administered sequentially at 20- to 30-minute intervals.

Subjects in Treatment Pathways 4 and 5 will have an OLFC after completing 12 months of Extended Maintenance treatment and may participate in an optional OLFC yearly thereafter and at the End of Treatment visit. Subjects in Treatment Pathways 1, 2, and 3 may participate in an optional yearly OLFC during the Extended Maintenance Period (ie, after completing 12 months of Extended Maintenance treatment and yearly thereafter) and the End of Treatment visit OLFC to assess the level of desensitization to peanut protein. Each OLFC during the Extended Maintenance Period will be conducted over a single day and in keeping with accepted food challenge procedures, will conditionally test 4 unblinded single doses sequentially at 20- to 30-minute intervals: 300 mg, 600 mg, 1000 mg, and 2000 mg of peanut protein using a defatted peanut flour.

The OLFC is described in detail in Appendix 10, including all requirements before, during, and after the OLFC. Full details are provided in the study procedures manual.

6.2.3 Double-Blind, Placebo-Controlled Food Challenge

A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. An optional DBPCFC will be performed after approximately 1 year of follow-up observation.

Each DBPCFC will be conducted over 2 days and consistent with accepted food challenge procedures. Single doses of peanut protein and placebo will be conditionally tested at the DBPCFC (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) using a food challenge mixture administered sequentially at 20- to 30-minute intervals up to a single highest challenge dose of 2000 mg (4043 mg cumulative).

The DBPCFC is described in detail in Appendix 11, including all requirements before, during, and after the DBPCFC. Subjects with allergy to oat or rice will not have the DBPCFC. Full details are provided in the study procedures manual.

6.3 Peanut Allergy Training

Peanut allergy training will be provided at each on-site visit as indicated in the Schedules of Events in the appendices and the provision of training recorded in the medical notes.

Subjects and parents/caregivers (as appropriate) will be instructed to continue to follow a peanut-avoidant diet. Subjects and parents/caregivers (as appropriate) will also receive training about food/peanut allergy according to the study site's established standards. This training will include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):

- Recognition of an allergic reaction and of the symptoms of anaphylaxis
- When and how to administer epinephrine via auto-injector

- Requirement to go to nearest emergency facility following use of epinephrine auto-injector
- Ways to minimize the risk of accidental exposure to peanut in and outside of the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)
- Investigators will train all subjects to adhere to a strict poststudy peanut elimination diet at the End of Treatment visit unless instructed otherwise

6.4 Lung Function, Asthma, Allergic Rhinitis, and Eczema/Atopic Dermatitis Assessments

6.4.1 Peak Expiratory Flow

The PEF should be measured at approximately the same time of day at each visit (eg, morning, afternoon, evening). The PEF will be measured in triplicate using a hand-held device at the visits indicated in the Schedules of Events in the appendices and the results recorded in the source document. The subject will be asked to stand and forcefully blow into the device 3 times. The best effort will be recorded in the electronic case report form (eCRF).

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

The ACT or C-ACT will be administered only to subjects with known asthma at the visits indicated in the Schedules of Events in the appendices during each visit and prior to the measurement of lung function. Results will be recorded in the source document.

The ACT (Schatz, 2006) is a self-administered 5-item questionnaire for subjects 12 years of age or older. It assesses the level of asthma control during the prior 4 weeks. Specifically, the test asks about shortness of breath, general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and the overall self-assessment of asthma control. Each question is scored with a 5-point scale, with lower numbers equating to worse control. The scores for each question are totaled, and a composite score of more than 19 indicates well-controlled asthma. Subjects who have turned 12 since entry into the ARC008 study will be asked to complete the ACT.

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

6.4.3 Test for Respiratory and Asthma Control in Kids (for Subjects Aged 1 to < 5 Years With Asthma in Treatment Pathways 4 and 5 Only)

In Treatment Pathways 4 and 5, asthma control in subjects aged 1 to < 5 years with pre-existing asthma will be assessed using TRACK scores and by the incidence of asthma rescue medication use. Subjects who turn age 5 years during the study or who are aged ≥ 5 years at enrollment in Treatment Pathways 4 and 5 will be administered the C-ACT questionnaire instead of the TRACK questionnaire.

The TRACK questionnaire will be administered at the visits indicated in the Schedule of Events (Appendix 4, Appendix 5). The parent/caregiver is to complete the TRACK, a 5-item standardized questionnaire used to evaluate respiratory and asthma control in children aged < 5 years with symptoms consistent with asthma (Zeiger, 2011). Each item is scored on a 5-point scale from 0 (4 or more times a week) to 20 (not at all). Higher scores indicate better respiratory and asthma control.

6.4.4 Asthma Evaluation for Subjects With Asthma in Treatment Pathways 4 and 5

Asthma evaluation will be performed for subjects with asthma at visits according to the Schedules of Events (Appendix 4, Appendix 5).

The evaluation of asthma severity will be assessed based on National Heart, Lung, and Blood Institute (NHLBI) classification, summarized in Table 8.

Table 8: Evaluation of Asthma Based on NHLBI Criteria (Treatment Pathways 4 and 5)

Classification	Intermittent (Step 1)	Persistent: Mild (Step 2)	Persistent: Moderate (Step 3 or 4)	Persistent: Severe (Step 5 or 6)
Subjects aged 0 to 4 years				
Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Night-time awakenings	0	1-2 times/month	3-4 times/month	> 1 time/week
Short-acting inhaled beta2-agonist use	≤ 2 days/week	> 2 days/week but not daily	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited

Classification	Intermittent (Step 1)	Persistent: Mild (Step 2)	Persistent: Moderate (Step 3 or 4)	Persistent: Severe (Step 5 or 6)
Subjects aged 5 to 11 years				
Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Night-time awakenings	≤ 2 times/month	3-4 times/month	> 1 time/week but not nightly	Often 7 times/week
Short-acting inhaled beta2-agonist use	≤ 2 days/week	> 2 days/week but not daily	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited

Adapted from NHLBI, 2007.
NHLBI, National Heart, Lung, and Blood Institute.

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

The TNSS (short form) will be administered only to subjects with known allergic rhinitis at the visits indicated in the Schedules of Events (Appendix 1, Appendix 2, Appendix 3).

It consists of 3 questions that address nasal obstruction, rhinorrhea, and nasal itch/sneezing. Each question has a choice of 4 responses that range from 0 (no symptoms) to 3 (severe symptoms). The subject is asked to recall symptoms over the last week to allow calculation of the symptom score.

6.4.6 Eczema Area and Severity Index (for Subjects With Eczema or Atopic Dermatitis in Treatment Pathways 4 and 5 Only)

For subjects with pre-existing eczema or atopic dermatitis, the severity of clinical signs of eczema or atopic dermatitis will be assessed using the EASI scoring system at visits according to the Schedules of Events (Appendix 4, Appendix 5). Higher scores indicate greater severity of eczema or atopic dermatitis.

6.5 Quality of Life and Treatment Satisfaction Assessments

The questionnaires will be administered to subjects at the visits indicated in the Schedules of Events in the appendices. The questionnaires should be completed before in-clinic dosing. The questionnaires may be completed during the observation period after completion of peanut protein administration as part of the OLFC.

Subjects may also be asked to complete health-related QoL questionnaires during the 1-year follow-up observation period.

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

The FAQLQ are questionnaires that measure health-related QoL in patients with food allergy. The following versions of the FAQLQ forms have been developed.

- Children 8 to 12 years of age (FAQLQ-CF) (Flokstra-de Blok, 2009)
- Adolescents 13 to 17 years of age (FAQLQ-TF) (Flokstra-de Blok, 2008)
- Adults 18 years of age and older (FAQLQ-AF) (van der Velde, 2009)
- Parents/caregivers of allergic children (FAQLQ-PF) (DunnGalvin, 2008)
- Parents/caregivers of allergic teenagers (FAQLQ-PFT)

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

For subjects aged ≤ 12 years, the parent/caregiver will complete the FAQLQ-PF. For subjects completing the FAQLQ-CF, subjects and parents/caregiver should be instructed to have the child provide his/her own responses. The parent/caregiver can help read the question or explain the meaning of the question, but the response should be selected only by the child.

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

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

6.5.2 Food Allergy Quality of Life-Parental Burden

The FAQL-PB is a 17-item self-administered questionnaire that measures QoL in caregivers for children with food allergy (Cohen, 2004). Each of the 17 questions is a 7-point Likert item, and the index is scored as a summated rating scale, with a higher FAQL-PB score indicating a worse QoL.

6.6 Immunologic Assessments

Blood samples for immunologic assessment will be collected at the visits indicated in the Schedules of Events in the appendices and analyzed at the central laboratory. Additional details for collecting, processing, and shipping these samples may be found in the Central

Laboratory Manual. Assessments include total, peanut-specific, and peanut component-specific serum IgE, and peanut-specific and peanut component-specific serum IgG4 levels.

6.7 Blood Volume

The blood volume collected in children aged 4 to 11 years will not exceed the total volume allowed by local ethical guidelines, or 5 mL/kg or a total of 50 mL in 8 weeks. The total volume of blood collected from subjects aged 1 to < 4 years is not to exceed 2 mL/kg per day (maximum 4 mL/kg in a 30-day period) or per local requirements. Blood samples will be collected in compliance with local laboratory guidelines and testing regulations.

6.8 Safety and Tolerability of AR101 Dosing

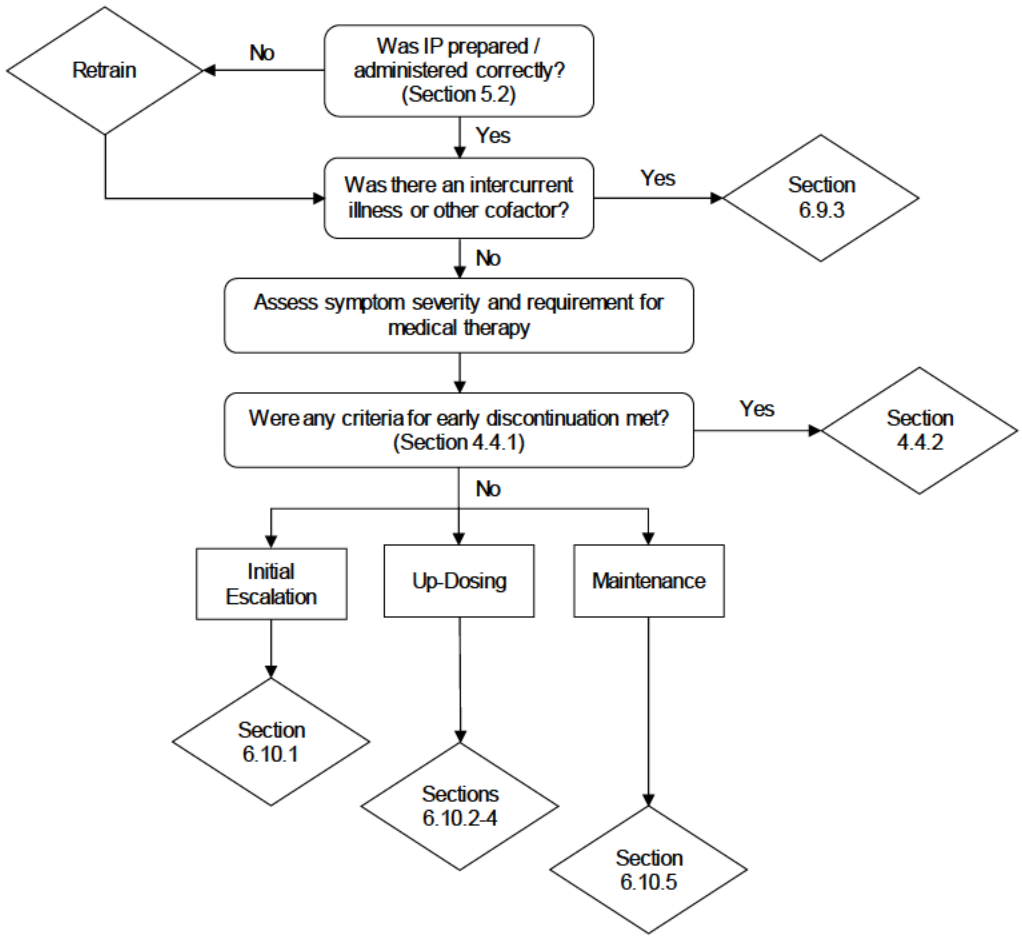
6.8.1 Overview

Subjects may develop allergic symptoms following a dose of AR101. Because AR101 contains peanut allergens, symptoms related to dosing are in general considered to be expected hypersensitivity adverse events, which is outlined further in the investigator brochure. Since most doses of AR101 will be given at home, much of the symptom reporting in this study will be second-hand. Given the reduced reliability inherent in this situation, investigators are strongly encouraged to have subjects return to the clinic to undergo dosing under direct observation whenever acute allergic symptoms associated with dosing are reported.

The initial step in evaluating the safety and tolerability of a dose or dose level is to determine how the dose was administered and under what clinical circumstances (eg, intercurrent AE, presence of a cofactor). The investigator must determine the severity of the reported or observed symptoms related to dosing using judgment and the CoFAR grading system for hypersensitivity AEs as a guide (Appendix 9). Once determined, the severity of allergic symptoms elicited at a particular AR101 dose will define the tolerability of that AR101 dose. In turn, the determination of tolerability will decide the course of action to be taken in response to reactions related to dosing. The period of the study and the location of the dose administration are also important in determining the next course of action, as illustrated in Figure 7 and summarized in text sections to follow and elsewhere in the protocol.

Certain allergy symptoms may be difficult to interpret in subjects aged < 4 years depending on their stage of development. Subtle symptoms may include ear picking, tongue rubbing, putting a hand in the mouth, and neck scratching (Bird, 2017). Other symptoms of allergic reaction may include persistent rubbing of the nose or eyes, irritability, clinging to the parent/caregiver, inconsolable crying, somnolence, and drawing legs up to the abdomen. The assessing physician will determine whether the allergy symptoms meet the criteria for dose-limiting symptoms (Section 6.8.2). The severity of symptoms of an allergic reaction will be assessed as described in Section 8.2.2.1.

Figure 7: Overview of Safety / Tolerability Assessment and Management



6.8.2 Assessment of the Tolerability of a Dose or Dose Level

Table 9 illustrates the relationship between symptom severity and tolerability of the dose. The greatest need for clinical judgment in determining the tolerability of a dose occurs when the dose elicits 1 or more mild allergic symptoms. The emergence of moderate and/or severe symptoms indicates that the dose was not tolerated.

Table 9: Allergy Symptom Severity and AR101 Dose Tolerability

Symptom Severity	Assessed Tolerability
None	Tolerated
Mild, oropharyngeal symptoms only	Tolerated
Mild, meeting predefined tolerability criteria (Appendix 9)	Tolerated [a]
Mild, **not** meeting predefined tolerability criteria (Appendix 9)	Not tolerated
Moderate (except for rare exceptions, Appendix 9)	Not tolerated
Severe	Not tolerated

Allergy symptoms may be difficult to interpret in subjects aged < 4 years depending on their stage of development. Age-appropriate allergy symptoms should be considered when assessing the tolerability of a dose.

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

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

- **No symptoms**: If a dose elicits no symptoms, the dose will be assessed as tolerated.
- **Mild symptoms**: When dosing with AR101 elicits an acute reaction characterized by the appearance of only a mild symptom(s), the investigator will be required to assess whether the dose was or was not tolerated. The determination of tolerability must be made based on clinical judgment. The following are presented as guidelines for determining whether a dose associated with the emergence of a mild symptom or symptoms was tolerated. A dose eliciting only mild symptoms may be considered to be tolerated if the symptoms are as follows:
  - Isolated to a single organ system
  - Resolve with no pharmaceutical intervention or with ≤ 2 doses of oral 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 and 3 studies, most acute allergic responses to dosing that are characterized by mild symptoms would be anticipated to meet the above criteria. Of note, GI symptoms were the most common potentially allergic symptoms to occur on a subacute, chronic, and/or recurrent basis in phase 2 and 3 clinical studies of AR101. If an allergic response to dosing is characterized by mild symptoms that do not meet all of the above criteria (eg, has mild symptoms occurring in 2 or more organ systems, requires treatment with 3 doses of oral H1 antihistamine or 1 dose epinephrine, shows progression in severity or distribution over time, is protracted in duration, or includes objective wheezing), then even though the allergic symptoms may be mild, the dose should be assessed as not tolerated. If a dose administered at home is suspected to have been not tolerated, even based on mild

symptoms, the subject should also return to the study site for dosing under medical supervision at the time of the next scheduled dose. If a dose elicits mild symptoms that do not fit all of the above criteria and the dose is assessed to be tolerated, then a brief explanation as to why the dose was considered tolerated must be recorded in the source documents.

The recurrence of a mild symptom(s) over the course of several days of home dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated, based on the criteria listed above. Further explanation follows; chronic/recurrent GI symptoms are given special consideration:

- If the study site is notified of mild symptoms related to dosing on 4 or more occasions during a single week during QD dosing, in the absence of an intercurrent AE, the subject should be brought to the study site for dosing under direct observation for assessment of the tolerability of the dose level.
- If mild symptoms related to dosing occur in the absence of an intercurrent illness and 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 6.9).
- Likewise, for Treatment Pathway 1 subjects on nondaily dosing regimens, if mild symptoms related to dosing occur in the absence of an intercurrent AE and are noted on ≥ 50% of the doses given over any 6-week period, that dose regimen should be considered not tolerated and appropriate action taken (see below).
- For any subject having chronic/recurrent GI symptoms, especially upper GI symptoms, investigators are advised to have a low threshold for instituting a dose reduction and/or for considering early discontinuation of affected subjects from the study even if mild, owing to the potential for EoE. Further specific instructions for this AEI can be found in Section 8.1.4.2.

- **Moderate symptoms**: In general, if a dose elicits moderate symptoms, the dose will be assessed as not tolerated. However, there may be rare occasions when a dose eliciting moderate symptoms could be assessed as tolerated. This would only be the case for a transient, self-limited (requiring no intervention and resolving completely) symptom occurring in a single organ system. In addition, the symptom would be typically subjective only. Any dose associated with moderate symptoms and assessed as tolerated must be accompanied by a brief explanation in the source documents as to why the dose was considered tolerated.
- **Severe symptoms**: If a dose elicits severe symptoms, the dose will be assessed as not tolerated. Whenever a dose elicits an allergic response characterized by 1 or more severe symptoms, the crucial decision, after adequate treatment for the allergic reaction has been administered, will be to determine whether the subject should continue in the study, dosing at a reduced dose level, or be discontinued early from the study.

Nondaily regimens (QOD, BIW, QW, or QOW) in Treatment Pathway 1 previously tolerated may eventually not be tolerated in ARC008. The inability to tolerate a nondaily regimen is

determined based on the criteria in Table 9. Mild, chronic GI symptoms may also be considered not tolerated (Section 8.1.4.2). Once a nondaily regimen in Treatment Pathway 1 is not tolerated, subjects must be transferred to Treatment Pathway 2 to down-dose and then undergo the modified dose-escalation procedure to a target of 300 mg QD; alternatively, the subject may be withdrawn from the study.

6.8.3 Dose Adjustment in Response to Intercurrent AEs (All Treatment Pathways)

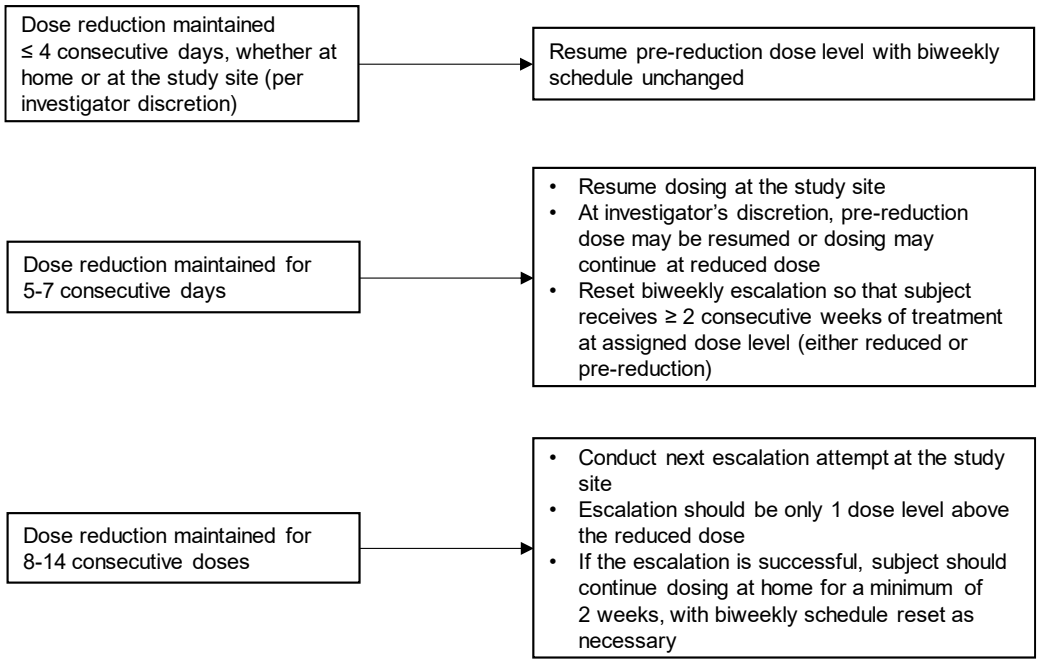
Emerging evidence from previously published OIT literature and phase 2 and 3 clinical studies of AR101 suggests that intercurrent illness may affect the tolerability of a dose. Section 5.2 provides guidelines around the preparation and administration of AR101, and outlines the importance of some of these known cofactors. Given that most AR101 doses are administered at home, sites are advised to educate subjects and families about these cofactors (some of which are AEs), as they may first become aware of an intercurrent AE that could create safety concerns. Subjects and/or caregivers should be encouraged to withhold the dose and call the study center for guidance if an intercurrent AE develops during the study. Occasionally the AE may only become clinically evident after the dose has already been given. In both cases, dose adjustments may be necessary and are discussed further below.

At the investigator's discretion, temporary dose reductions ranging from a 1-step decrement (ie, to the previous dose) to approximately half of the current dose level (to the nearest feasible available whole dose) can be instituted as part of the treatment regimen for an intercurrent AE. Also, if a pattern of decreased tolerability of study product during menses is discerned, then a temporary dose reduction can be instituted during this time.

As an alternative to dose reduction, AR101 may also be temporarily withheld at the investigator's discretion, in response to an intercurrent AE. In some cases (eg, when the intercurrent AE is clinically significant) this may be the most appropriate course of action. Dosing after missed or withheld doses should follow the guidance provided in Section 5.4.

A schematic showing procedures for temporary dose reductions due to intercurrent AEs is provided in Figure 8; explanatory text follows the figure.

Figure 8: Schematic for Temporary Dose Reductions due to Intercurrent Adverse Events (QD Regimens Only)



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

Doses withheld as part of the treatment for an AE constitute a distinct category of missed peanut OIT doses. Dosing after missed or withheld doses should follow the guidance provided in Section 5.4.

6.9 Assessing Symptoms During In-Clinic or Home Dosing by Study Period

Symptoms related to dosing in ARC008 may vary by study period and by in-clinic administration or administration at home. In-clinic dosing occurs most frequently during the Initial Escalation (Treatment Pathways 3 and 5) and Up-Dosing (Treatment Pathways 2, 3, and 5) Periods, and periodically during the Maintenance Period (all Treatment Pathways). These doses are administered under direct observation in monitored settings, and only after study procedures that ensure the subject is in general baseline health (eg, a physical examination and PEF). If a subject has a dose escalation in the clinic without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the clinic for the next scheduled visit. However, if symptoms arise in the clinic after observed dosing, the investigator will determine whether the dose was tolerated (Section 6.8.2). The process algorithm for continued dosing after symptoms related to dosing occur in the clinic depends on the study period and is described below and shown in Figure 8.

Allergy symptoms may be difficult to interpret in subjects aged < 4 years depending on their stage of development. Age-appropriate allergy symptoms should be considered when determining the appropriate actions to be taken with study product dosing.

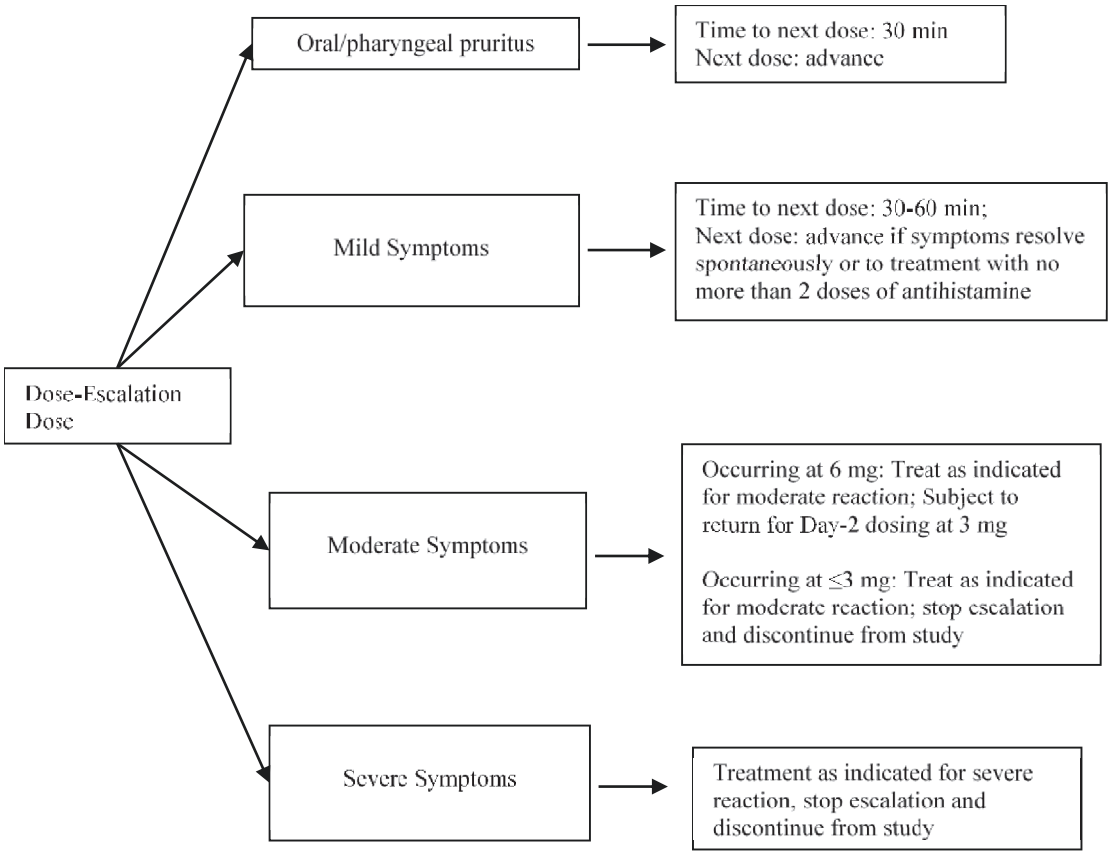
6.9.1 Management of In-Clinic Symptoms Related to Dosing During Initial Escalation Period (Treatment Pathways 3 and 5)

The algorithm for responding to acute allergic symptoms during the in-clinic Initial Escalation, Day 1, is shown in Figure 9. Explanatory text follows the figure.

An Aimmune medical monitor will be available to answer any questions or to assist in any decisions related to the study protocol. Investigator judgment will be required to determine the best course of action, with possible actions as shown 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, inhaled beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids, as necessary, and discontinuing dose escalation
- Early discontinuation

Figure 9: Schematic for 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, if symptoms have resolved to the point where the investigator assesses the subject to be safe to continue dosing (ie, having no or only minimal residual signs or symptoms)

  In general, if a subject requires only 1 or 2 doses of antihistamine to treat mild symptoms occurring during the initial escalation, then the initial escalation may continue. If, however, the subject requires a second medication (eg, epinephrine or an inhaled 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 symptoms related to dosing, even in the unlikely event that the symptoms are graded as mild, will be cause to terminate the initial escalation.

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

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

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

6.9.2 Management of In-Clinic Symptoms Related to Dosing During Up-Dosing Period (Treatment Pathways 2, 3, and 5): First Dose Tolerated at New Dose Level

The scenarios listed below describe a subject in the Up-Dosing Period who has symptoms but is considered to have tolerated the first dose at a new dose level. The procedures outlined for each scenario should be followed.

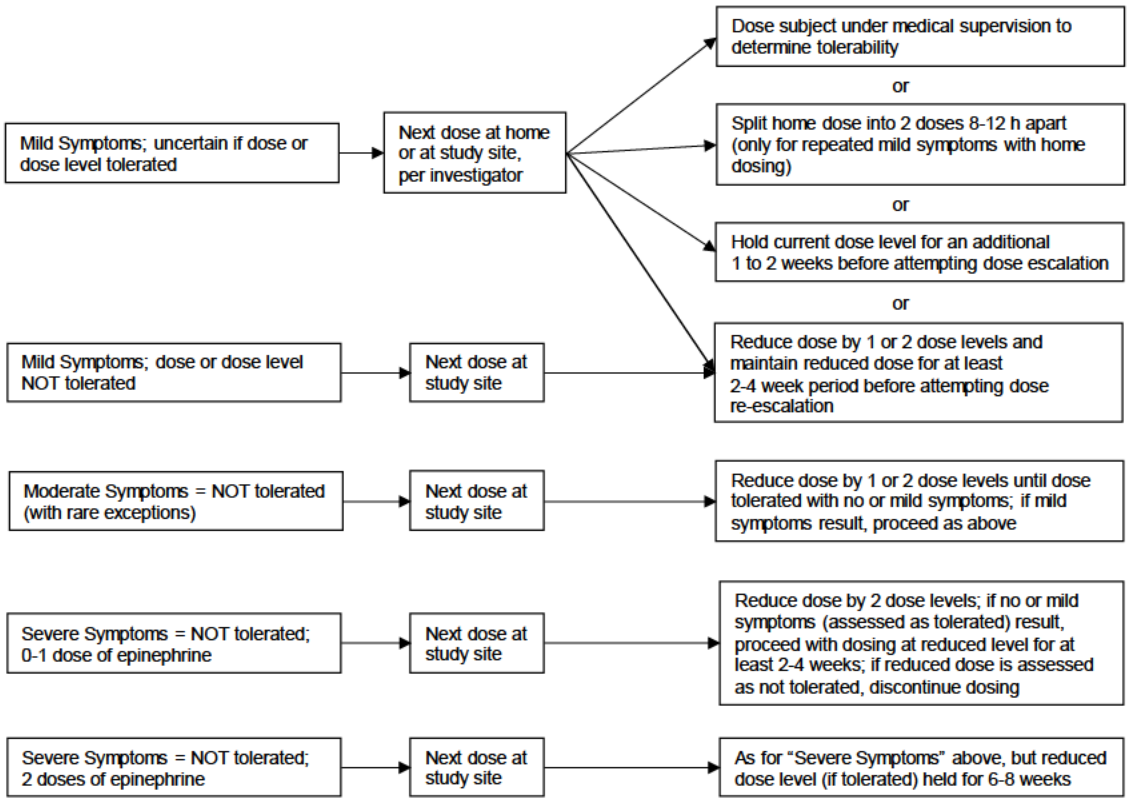
- No symptoms: If a subject undergoes up-dosing at the study site without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the study site for the next scheduled dose escalation visit 2 weeks later.
- Oral/pharyngeal pruritus only: 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 (Section 6.9).
- Mild symptoms tolerated at first dose at new dose level: If *mild symptoms* (Section 6.8) 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 at the study site, but it may be given at home, at the investigator's discretion. If the second dose at the new (increased) dose level is tolerated without symptoms, then the subject is to continue

on that dose level for the requisite 2 weeks and return for up-dosing at the next scheduled visit at the study site. 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 6.9.4 and Section 6.9.5 for actions to be taken if 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 Section 6.8.2 should be followed.

6.9.3 Management of In-Clinic Symptoms Related to Dosing During Up-Dosing Period (Treatment Pathways 2, 3, and 5): Tolerability Uncertain or No Tolerability at First Dose at New Dose Level

If a subject has symptoms after up-dosing at the study site that suggest the dose was not tolerated, or that toleration of the dose is uncertain, the investigator must assess the tolerability, as outlined in Section 6.8.2. The algorithm for continued dosing if symptoms occur after the first dose at a new dose level that indicate uncertainty regarding tolerability or lack of tolerability is depicted in Figure 10. Explanatory text follows the figure. Dose adjustment after administration of antihistamines and/or epinephrine for allergy symptoms related to dosing is described in Section 6.10.

Figure 10: Schematic for Treatment of Reactions Indicating Uncertain Tolerability or Lack of Tolerability During the Up-Dosing Period



- Mild symptoms that indicate uncertainty regarding tolerability: If *mild symptoms* (Section 6.8.2), 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 at the study site 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 study site. 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 the next day for dosing at the last tolerated dose (ie, a 1-step dose reduction) under medical supervision at the study site (if the subject is unable to return on the day specified, the investigator may initiate an approximate 1 dose-level reduction at home, with the subject coming to the study site at the earliest date possible).

  If the reduced dose is *assessed as tolerated*, the subject is to continue on that daily home dose for the ensuing 2 weeks. (See Section 6.9.4 and Section 6.9.5 for actions to be taken if symptoms develop during home-dosing.) If the reduced dose is again *assessed as not tolerated*, the subject is to return the next day for supervised dosing at

a 1- or 2-step reduction in dose (per investigator judgment, based on severity of reaction) at the study site. 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 will discontinue study treatment.

- Moderate symptoms (these indicate lack of tolerability, with rare exceptions): On rare occasions, a transient, self-limited (requiring no intervention and resolving completely) symptom of moderate intensity occurring in a single organ system may be assessed as tolerated. 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; (see Section 6.8.2, for moderate symptoms assessed as tolerated): If *moderate symptoms* occur with the first dose at a new dose level, except for rare instances, the dose will be *assessed as not tolerated*. The action taken should be to have the subject return the next day for dosing at the last tolerated dose under medical supervision at the study site. If this reduced dose elicits no allergic symptoms (ie, is well tolerated), the subject will continue on that daily home dose level for an additional 2 weeks.

  If the subject experiences mild symptoms at the reduced dose, the procedures for responding to a dose with mild symptoms should be followed (see above). If the subject experiences moderate symptoms at the reduced dose level, the subject should return the next day and receive a further 1- or 2-step dose reduction (per investigator judgment) at the study site. If this reduced dose is well tolerated, it will be continued as the daily home dose for ≥ 2 weeks before re-escalation is attempted at the study site. 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 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 the next day for dosing at a 2-step reduction in dose under observation at the study site. 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 attempting dose re-escalation at the study site. If the subject does not tolerate the reduced dose, then the subject will discontinue study treatment.

  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 study site 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.

6.9.4 Management of Symptoms Related to Dosing During Up-Dosing Period After the First Dose (Treatment Pathways 2, 3, and 5)

Whereas the Initial Escalation Period occurs exclusively at the study site, most doses of AR101 will be given at home during the Up-Dosing and Maintenance Periods of ARC008. With the occurrence of symptoms of an acute reaction to AR101 after home dosing, or any acute allergic reaction, subjects or parents/caregivers are instructed to call the study site personnel. When symptoms of an allergic reaction related to dosing are reported during the course of daily home-dosing in any period, the investigator must assess the severity of the reaction and whether the dose associated with the reaction was tolerated (Table 9). 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. If a previously tolerated dose or dose level is subsequently assessed *as not tolerated*, the action taken will depend on the type and severity of the reaction related to dosing and the investigator's clinical judgment. The following possible actions are described and also shown in Figure 10:

- Dosing the subject under medical supervision at the study site – 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-dosing 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 at the study site 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 anytime and for any reason. The investigator must discontinue the subject from further dosing and continuation in the study under circumstances that could jeopardize the health of the subject or the integrity of the study.

For any subject having chronic/recurrent GI symptoms, especially upper GI symptoms, investigators are advised to have a low threshold for instituting a dose reduction and/or for considering early discontinuation of affected subjects from the study even if mild, owing to the potential for EoE. Further specific instructions for this AEI are provided in Section 8.1.4.2.

Dose adjustment after administration of antihistamines and/or epinephrine for allergy symptoms related to dosing is described in Section 6.10.

6.9.5 Management of Symptoms Related to Dosing Occurring During Maintenance Period (All Treatment Pathways)

Dosing guidelines following treatments given for reactions experienced by subjects in all Treatment Pathways receiving AR101 at 300 mg QD, QOD, BIW, QW, or QOW during the Maintenance and Extended Maintenance period are summarized in Table 10. A textual explanation follows the table. Dose adjustment after administration of antihistamines and/or epinephrine for allergy symptoms related to dosing is described in Section 6.10.

Table 10: Dose Adjustments Following Symptoms Related to Dosing Experienced by Subjects Receiving AR101 at 300 mg QD, QOD, BIW, QW, or QOW During Maintenance and Extended Maintenance

Treatment Regimen	Dosing Guidelines and Procedures
QD	Use up-dosing procedures (Section 6.9.3, Section 6.9.4).
QOD, BIW, QW, or QOW	• For intercurrent AEs and symptoms related to dosing, hold the scheduled dose until the AE is resolved and the dose can be safely administered. – Reset the interval between doses once the subsequent dose is tolerated. – If the dose must be held 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. • Subjects may be transferred to Treatment Pathway 2 anytime if impaired tolerability of the dosing regimen develops (Section 3.1.1); and they will be transferred to Treatment Pathway 2 following the occurrence of any of the following: – 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"

The investigator should assess the benefit-risk of continued AR101 treatment when a subject has several AR101-related systemic allergic reactions (anaphylactic events) during maintenance treatment.

AE, adverse event; BIW, twice weekly; QD, once daily; QOD, every other day; QOW, every other week; QW, once weekly; SAE, serious adverse event.

- This study period consists of the subject receiving the 300 mg dose of study product QD, QOD, BIW, QW, or QOW. For any noted symptoms during the QD Initial Maintenance or Extended Maintenance 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 investigator should assess the benefit-risk of continued AR101 treatment when a subject has several AR101-related systemic allergic reactions (anaphylactic events) during maintenance treatment.
- The tolerability of doses on nondaily dosing regimens will be evaluated as in Section 6.8 and Table 10. 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 hold 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 held 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 the same Treatment Pathway and administer the next 300 mg dose under supervision at the study site.
    a. If tolerated, continue EM dosing at 300 mg on the same schedule, resetting the dosing interval;
    b. If not tolerated, consider options 2 or 3 below.
2. Continue the same Treatment Pathway and administer approximately half of the 300 mg dose under supervision at the study site. 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 Treatment Pathway 1 and switch to Treatment Pathway 2, initiating the dose reduction and modified escalation procedure described in Section 7.2.2. This should be the preferred option for any QOD, BIW, or QW subject who had missed 4 or more scheduled doses and/or whose interval between AR101 exposures exceeds 14 days.
4. Discontinue ARC008.

- For subjects having acute reactions to QOD, BIW, QW, or QOW doses, the next action will be determined by symptom severity. As mentioned in Section 3.1.1 any Extended Maintenance 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 transferred from Treatment Pathway 1 to Treatment Pathway 2 for safety reasons. Such subjects will undergo the dose reduction and modified escalation procedure described in Section 7.2.2 in order to return to a 300 mg QD regimen. Alternatively, they may be discontinued from the study.

6.10 Treatment for Dosing Reactions: Pharmacological and Supportive Therapy

Treatment for allergic reactions during the study is guided by the type of symptoms and severity as determined by the investigator.

- Treatment for acute reactions should be provided according to the standard of allergy care, with 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. This will usually consist of antihistamines and/or epinephrine, as indicated. If there is uncertainty as to the severity of the reaction, administering epinephrine would be considered the most appropriate course of action.

The procedures that should be implemented after treatment of a reaction to an AR101 dose during the study are summarized in Table 11. An explanation follows the table.

Table 11: Procedures Following Treatment of a Dosing Reaction

Treatment Given for Reaction	Procedures Following Treatment
≤ 2 doses of antihistamines	Continue dose escalation if in Initial Escalation / Up-Dosing Period
Epinephrine: > 2 doses either in clinic or at home	Subject returns to clinic, undergoes Early Discontinuation visit, discontinues treatment
Epinephrine: single dose given in clinic	• Stop dosing at clinic • Reduce next dose by 2 dose levels and administer in clinic • Continue biweekly escalation
Epinephrine required for a second consecutive time during, or after, 1 escalation attempt	• Reduce next dose by 2 dose levels and administer in clinic • 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 clinic 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 • Reduce next dose by 1 or 2 dose levels and administer in clinic under medical supervision prior to resuming any dosing at home

- Antihistamines Given

  If a subject receives 2 or fewer doses of antihistamines only, the dose escalation can be continued. If more than 2 doses of antihistamine, or epinephrine, or a combination of medications, is administered, then a different course of action is to be taken.

  If symptoms during up-dosing at the study site or at home require > 2 doses of antihistamine alone or in combination with other medications (except epinephrine), reduce the next dose of study product by 1 or 2 dose levels and give it at the study site under medical supervision. If no symptoms occur at the reduced dose, continue up-dosing for the 2-week dosing interval.

- Epinephrine – General Procedures

  Any reaction to study product (in clinic or at home) that requires more than 2 doses of epinephrine will stop all further dosing of study product for the individual. The subject will be asked to return 14 days following the last dose of study product for an Early Discontinuation visit (Section 4.4).
- 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 at the study site, 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 same dose level continued for 6 to 8 weeks. After 6 to 8 weeks at the reduced dose, an escalation may be attempted in the clinic.

  If a single administration of epinephrine is required for a third consecutive time during an escalation attempt, no further dosing should be attempted and dosing will be discontinued. Subjects will be asked to return 14 days following their last dose of study product for an Early Discontinuation visit (Section 4.4).
- 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 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 next dose of AR101 is to be reduced by 1 or 2 dose levels and administered in the clinic under medical supervision prior to resuming any dosing at home.

7 STUDY VISITS

Enrollment and study procedures are summarized in the following subsections.

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

Enrollment and study procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

7.1 Treatment Pathway 1

7.1.1 Screening/Baseline Visit

Before any unique ARC008-related procedures are performed, the investigator or designee must obtain written informed consent/assent for this study from the subject and parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline visit occurs on the same day (+3 days) as the exit visit of the parent study unless specified

otherwise in the parent study protocol, and must be completed within 28 days after the signing of the informed consent form (ICF)/assent form. Initiation of AR101 treatment in this study must be within 3 days after the Exit visit of the parent study for subjects treated with AR101 in the parent study, unless specified otherwise in the parent study protocol. The first dose of AR101 in ARC008 should not be administered on the same day as an exit food challenge or dosing in the parent study.

The following Screening/Baseline procedures will be conducted as part of ARC008 if not completed at the parent study Exit visit (or other visit if specified). A detailed list of Screening/Baseline procedures to be performed as part of ARC008 based on each parent study is provided as a guide in Appendix 1. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 1.

- Inclusion/exclusion criteria review
- Demographics
- Medical and allergy history review
- Concomitant medication review
- Food allergen exposure update
- Complete physical examination, including weight and height
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon, evening])
- Blood sample collection:
  - Complete blood count (CBC)
  - Immunology assessments
- Serum pregnancy test (for sexually active females of childbearing potential only)
- SPT
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (complete before PEF)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM

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

- AE recording (including allergic symptoms)
- Peanut allergy training
- In-clinic dosing, unless the visit occurs on the same day as an exit food challenge or dosing in the parent study
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.1.2 Extended Maintenance Period (Visits Every 3 Months)

In the Extended Maintenance Period, clinic visits will occur every 3 months ±2 weeks (with the first visit designated as Month 3) until the end of treatment (early discontinuation or study completion).

The following procedures will be performed before administration of each in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Physical examination (complete physical examination with weight and height at 6-month intervals [Month 6, 12, 18, etc, visits] only; abbreviated physical examination at other visits)
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (at annual visits [Months 12, 24, 36, etc] only)
  - Immunology assessments (at annual visits [Months 12, 24, 36, etc] only)
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT (at annual visits [Months 12, 24, 36, etc] only)
- Completion of questionnaires (at annual visits only):
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- Completion of questionnaires (at 6-month intervals [Month 6, 12, 18, etc, visits] only):
  - FAQLQ and FAIM

After completion of these procedures, for subjects not undergoing OLFC, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

After 12 months of treatment during Extended Maintenance and yearly thereafter, an OLFC will be conducted for subjects who have consented to this procedure (Appendix 10). AR101 will not be administered to these subjects on the day of their OLFC.

The following procedures will be performed before discharge from the clinic (regardless of completion of the OLFC):

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.1.3 End of Treatment Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of AR101 treatment, subjects will return to the clinic for the End of Treatment visit. A DBPCFC (Appendix 11) will be performed for all subjects except those who discontinue early for safety reasons. AR101 will not be administered on the days of the DBPCFC. AR101 dosing will continue until the last food challenge is performed.

The following procedures will be performed before the DBPCFC:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Complete physical examination, including weight and height
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (if not completed within prior 6 months)
  - Immunology assessments
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT
- PEESS v2.0 (for subjects who had GI AEIs)

- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training

At the end of the End of Treatment visit, the investigator must advise the subject or parent/caregiver of appropriate options for continued management of peanut allergy.

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone at least 14 days after the last AR101 dose or last food challenge, whichever is last, to enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic and to provide assistance in management of events.

7.1.4 Unscheduled Visit

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

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

7.1.5 Unscheduled Blood Sample

An unscheduled blood sample for CBC and immunologic assessments may be collected around the time of the last dose of AR101 during a scheduled or unscheduled visit for subjects who intend to discontinue dosing; a blood sample will not be required at the End of Treatment visit if this unscheduled blood sample is collected.

7.1.6 Follow-Up Observation Period

The End of Treatment visit will be followed by a 12-month observation period (Appendix 6). During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan
- Key events review

7.1.7 Study Exit Visit

The Study Exit visit will be conducted at 12 months after the last dose of AR101 (Appendix 6). An optional DBPCFC may be performed.

The following procedures will be performed:

- Verification of informed consent/assent for participation in the DBPCFC
- Height, weight
- Vital signs
- PEF
- Current treatment plan
- Key events review
- Abbreviated physical examination
- Blood sample collection for immunology assessments
- SPT
- FAQLQ and FAIM questionnaires

After completing these procedures, a DBPCFC will be performed for subjects who consent.

7.2 Treatment Pathway 2

7.2.1 Screening/Baseline Visit

Before any unique ARC008-related procedures are performed, the investigator or designee must obtain written informed consent/assent for this study from the subject and parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline visit must be completed within 28 days after the signing of the ICF/assent form. Initiation of AR101 treatment in this study must be within 3 days after the Early Discontinuation visit of the parent study, unless specified otherwise in the parent study protocol. The first dose of AR101 in ARC008 should not be administered on the same day as dosing in the parent study.

Subjects who enter ARC008 on Treatment Pathway 1 but do not tolerate nondaily dosing and switch to Treatment Pathway 2 do not need to undergo the Screening/Baseline visit for Treatment Pathway 2. They will proceed directly to the Repeat Up-Dosing visit as described in Section 7.2.2.

The following Screening/Baseline procedures will be conducted as part of ARC008 if not completed at the parent study Early Discontinuation visit (or other visit if specified).
A detailed list of Screening/Baseline procedures to be performed as part of ARC008 based on each parent study is provided as a guide in Appendix 2. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 2.

- Inclusion/exclusion criteria review
- Demographics

- Medical and allergy history review
- Concomitant medication review
- Food allergen exposure update
- Complete physical examination, including weight and height
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon, evening])
- Blood sample collection:
- CBC
- Immunology assessments
- Serum pregnancy test (for sexually active females of childbearing potential only)
- SPT
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM
- In-clinic dosing for subjects who continued AR101 treatment in the parent study, unless the visit occurs on the same day as dosing in the parent study
- AR101 dispensing (for subjects who continued AR101 treatment in the parent study)
- Home dosing instruction (Section 5.2)
- AE recording (including allergic symptoms)
- Peanut allergy training

The Repeat Up-Dosing Period should start on the same day as the Screening/Baseline visit to ensure continuity of AR101 dosing. The start of the Repeat Up-Dosing Period may be delayed at the investigator's discretion in accordance with the guidelines in Section 7.2.2.

Site staff will contact the subject or subject's parent/caregiver by telephone within 2 days after the visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.2.2 Up-Dosing/Repeat Up-Dosing Period

Subjects who did not complete their AR101 up-dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue up-dosing in ARC008, with dose escalation approximately every 2 weeks up to the 300 mg maximum daily dose. The first dose at each new dose level will be administered under medical supervision in the clinic; the remaining doses at each dose level will be administered daily at home as tolerated.

Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit in ARC008 and then enter a Repeat Up-Dosing Period, starting with a daily dose of AR101 at 80, 120, or 160 mg/day, at the investigator's discretion. The dose will be increased every 2 weeks until the maximum daily dose of 300 mg/day is reached. The Repeat Up-Dosing Period comprises scheduled visits every 2 weeks ±2 days at which the first dose at each new dose level will be administered in the clinic.

Unscheduled visits may be conducted for assessment of dose tolerability, dose reduction, or dose re-escalation or management of AEs.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness before administration of the in-clinic dose. Subjects should be maintained on the current or a reduced dose level of AR101 until the active wheezing, flare of atopic disease, or intercurrent illness has resolved.

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

The following guidelines for dose escalation and reduction will be followed during the Up-Dosing Period:

- 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, the 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 6.8 with the dose adjustment depending on the severity of the symptoms related to dosing.
- Subjects who require dose reduction during a 2-week period between visits will have the 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 within the next 4 weeks unless escalation is to be delayed further because of administration of epinephrine (Section 6.10). Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced at least 2 weeks apart, will result in the discontinuation of dosing. The subject will have the End of Treatment visit (Section 7.2.5).

7.2.2.1 Up-Dosing Visits

The following procedures will be performed before administration of each in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms (not required at first up-dosing visit if on the same day as Screening/Baseline visit)
- Concomitant medication review (not required at first up-dosing visit if on the same day as Screening/Baseline visit)
- Food allergen exposure update (not required at first up-dosing visit if on the same day as Screening/Baseline visit)
- Return of unused AR101 (not required at first up-dosing visit)
- AR101 dosing compliance check (not required at first up-dosing visit)
- Physical examination (not required at first up-dosing visit if on the same day as Screening/Baseline visit).
  - Complete physical examination, with weight and height, at first up-dosing visit, if required, and at the 300 mg visit,
  - Abbreviated physical examination at other visits
- Vital signs (not required at first up-dosing visit if on the same day as Screening/Baseline visit)
- Urine pregnancy test, for sexually active females of childbearing potential only, at 300 mg visit only. Not required at first up-dosing visit if on the same day as Screening/Baseline visit
- Completion of questionnaires (not required at first up-dosing visit if on the same day as Screening/Baseline visit):
  - ACT/C-ACT, for subjects with known asthma only, at 80 mg visit only (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- PEF should be measured at approximately the same time of day at each visit assessment. Not required at first up-dosing visit if on the same day as Screening/Baseline visit

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.1 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject or subject's parent/caregiver by telephone within 2 days after the visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.2.2.2 End Up-Dosing Visit

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Abbreviated physical examination
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC
  - Immunology assessments
- SPT
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.1 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone 3 to 5 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms GI symptoms, and accidental/nonaccidental food

allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.2.3 Initial Maintenance Period (Visits Every 8 Weeks for 24 Weeks)

Subjects who did not complete their AR101 maintenance regimen in an eligible parent study will have a Screening/Baseline visit and begin the Initial Maintenance Period in ARC008.

In the Initial Maintenance Period, clinic visits will occur every 8 weeks ±1 week for 24 weeks (with the first visit designated as Week 8).

Subjects should withhold their daily home AR101 dose on in-clinic dosing days but should take all other prescribed medications as scheduled.

The guidelines for dose escalation and reduction are the same as during the Up-Dosing Period (Section 7.2.2).

7.2.3.1 Week 8 and Week 16

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Abbreviated physical examination
- Vital signs
- Urine pregnancy test, for sexually active females of childbearing potential only, at Week 8 only
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- PEF (should be measured at approximately the same time of day at each visit assessment)

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training

- AR101 dispensing
- Home dosing instruction (Section 5.2)

7.2.3.2 Week 24

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Complete physical examination
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC
  - Immunology assessments
- Urine pregnancy test (for sexually active females of childbearing potential only)
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.2.4 Extended Maintenance Period (Visit Every 3 Months)

In the Extended Maintenance Period, clinic visits will occur every 3 months ±2 weeks (with the first visit designated as Month 3) until the end of treatment (early discontinuation or study completion).

The following procedures will be performed before administration of each in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Physical examination
  - Complete physical examination, with weight and height, at 6-month intervals (Month 6, 12, 18, etc, visits) only;
  - Abbreviated physical examination at other visits
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (at annual visits [Months 12, 24, 36, etc] only)
  - Immunology assessments (at annual visits [Months 12, 24, 36, etc] only)
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT (at annual visits [Months 12, 24, 36, etc] only)
- Completion of questionnaires (at annual visits only):
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- Completion of questionnaires (at 6-month intervals [Month 6, 12, 18, etc. visits] only):
  - FAQLQ and FAIM

After completion of these procedures, for subjects not undergoing OLFC, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

After 12 months of treatment during Extended Maintenance and yearly thereafter, an OLFC will be conducted for subjects who have consented to this procedure (Appendix 10). AR101 will not be administered to these subjects on the day of their OLFC.

The following procedures will be performed before discharge from the clinic (regardless of completion of the OLFC):

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.2.5 End of Treatment Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of AR101 treatment, subjects will return to the clinic for the End of Treatment visit. A DBPCFC (Appendix 11) will be performed for all subjects except those who discontinue early for safety reasons. AR101 will not be administered on the days of the DBPCFC. AR101 dosing will continue until the last food challenge is performed.

The following procedures will be performed before the DBPCFC:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Complete physical examination, including weight and height
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (if not completed within prior 6 months)
  - Immunology assessments
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT
- PEESS v2.0 (for subjects who had GI AEIs)

- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training

At the end of the End of Treatment visit, the investigator must advise the subject or parent/caregiver of appropriate options for continued management of peanut allergy.

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone at least 14 days after the last AR101 dose or last food challenge, whichever is last, to enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic and to provide assistance in management of events.

7.2.6 Unscheduled Visit

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

The procedures performed at unscheduled visits may include any or all of those listed in Appendix 2.

7.2.7 Unscheduled Blood Sample

An unscheduled blood sample for CBC and immunologic assessments may be collected around the time of the last dose of AR101 during a scheduled or unscheduled visit for subjects who intend to discontinue dosing; a blood sample will not be required at the End of Treatment visit if this unscheduled blood sample is collected.

7.2.8 Follow-Up Observation Period

The End of Treatment visit will be followed by a 12-month observation period (Appendix 6). During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan
- Key events review

7.2.9 Study Exit Visit

The Study Exit visit will be conducted at 12 months after the last dose of AR101 (Appendix 6). An optional DBPCFC may be performed.

The following procedures will be performed:

- Verification of informed consent/assent for participation in the DBPCFC
- Height, weight
- Vital signs
- PEF
- Current treatment plan
- Key events review
- Abbreviated physical examination
- Blood sample collection for immunology assessments
- SPT
- FAQLQ and FAIM questionnaires

After completing these procedures, a DBPCFC will be performed for subjects who consent.

7.3 Treatment Pathway 3

7.3.1 Screening/Baseline Visit

Before any unique ARC008-related procedures are performed, the investigator or designee must obtain written informed consent/assent for this study from the subject and parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline visit must be completed within 28 days after the signing of the ICF/assent form.

The following Screening/Baseline procedures will be conducted as part of ARC008 if not completed at the parent study Exit visit (or other visit if specified). A detailed list of Screening/Baseline procedures to be performed as part of ARC008 based on each parent study is provided as a guide in Appendix 3. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 3.

- Inclusion/exclusion criteria review
- Demographics
- Medical and allergy history review
- Concomitant medication review
- Food allergen exposure update
- Complete physical examination, including weight and height
- Vital signs

- PEF (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon, evening])
- Blood sample collection:
  - CBC
  - Immunology assessments
- Serum pregnancy test (for sexually active females of childbearing potential only)
- SPT
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM
  - FAQL-PB
- AE recording
- Peanut allergy training

The site staff will schedule the Initial Escalation Period visits. Day 1 should occur within 10 days after the Screening/Baseline visit.

7.3.2 Initial Escalation Period

If the Initial Escalation Period is not started within 10 days after the Screening/Baseline visit, written approval to rescreen the subject and/or to waive any of the Screening/Baseline procedures must be obtained from a medical monitor.

7.3.2.1 Day 1

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), and suspected intercurrent illness before initiating dose escalation. Additionally, subjects must be fully recovered (ie, back to baseline state of health) from any preceding illness for at least 3 days, depending on the investigator-determined severity of the illness.

Subjects may have clear liquids or flavored gelatin during the escalation procedure while the desensitization doses are administered.

The following procedures will be performed before dose escalation:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Abbreviated physical examination
- Vital signs

- Completion of questionnaires:
  - TNSS (for subjects with known allergic rhinitis only)
- PEF (should be measured at approximately the same time of day at each visit assessment)

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.2.1.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training

7.3.2.2 Day 2 (Day After Day 1)

The only exception to Day 2 immediately following Day 1 is when unforeseen circumstances (eg, an intercurrent illness) create a safety risk to provide the next dose, consistent with the rules for missed doses (Section 5.4). If such a circumstance occurs, the investigator must discuss the case with a medical monitor before administering the next dose.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness before administration of the confirmatory dose.

The following procedures will be performed before administration of the confirmatory dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Abbreviated physical examination
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.2.2.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone within 2 days after the visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.3.3 Up-Dosing Period (Visits Every 2 Weeks for 22 to 52 Weeks)

The Up-Dosing Period comprises 11 scheduled visits (including the end of up-dosing visit) every 2 weeks ±2 days at which the first dose at each new dose level will be administered in the clinic. Unscheduled visits may be conducted for assessment of dose tolerability, dose reduction, or dose re-escalation or management of AEs.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness before administration of the in-clinic dose. Subjects should be maintained on the current or a reduced dose level of AR101 until the active wheezing, flare of atopic disease, or intercurrent illness has resolved.

Subjects should withhold their daily home dose of AR101 on in-clinic dosing days but should take all other prescribed medications as scheduled.

The following guidelines for dose escalation and reduction will be followed during the Up-Dosing Period:

- 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, the 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 6.8 with the dose adjustment depending on the severity of the symptoms related to dosing.
- Subjects who require dose reduction during a 2-week period between visits will have the 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 within the next 4 weeks unless escalation is to be delayed further because of administration of epinephrine (Section 6.10). Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced at least 2 weeks apart, will result in the discontinuation of dosing. The subject will have the End of Treatment visit (Section 7.3.6).

7.3.3.1 Up-Dosing Visits

The following procedures will be performed before administration of each in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Physical examination
  - Complete physical examination, with weight and height, at 80 mg and 300 mg visits
  - Abbreviated physical examination at other visits
- Vital signs
- Urine pregnancy test (for sexually active females of childbearing potential only) (at 300 mg visit only)
- Completion of questionnaires:
  - ACT/C-ACT, for subjects with known asthma only, at 80 mg visit only (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- PEF (should be measured at approximately the same time of day at each visit assessment)

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone within 2 days after the visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.3.3.2 End Up-Dosing Visit

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Abbreviated physical examination
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC
  - Immunology assessments
- SPT
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM
  - FAQL-PB

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Telephone contact: Site staff will contact the subject or subject's parent/caregiver by telephone 3 to 5 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.3.4 Initial Maintenance Period (Visits Every 8 Weeks for 24 Weeks)

In the Initial Maintenance Period, clinic visits will occur every 8 weeks ±1 week for 24 weeks (with the first visit designated as Week 8).

Subjects should withhold their daily home AR101 dose on in-clinic dosing days but should take all other prescribed medications as scheduled.

The guidelines for dose escalation and reduction are the same as during the Up-Dosing Period (Section 7.3.3).

7.3.4.1 Week 8 and Week 16

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Abbreviated physical examination
- Vital signs
- Urine pregnancy test, for sexually active females of childbearing potential only. Week 8 only
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- PEF (should be measured at approximately the same time of day at each visit assessment)

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

7.3.4.2 Week 24

The following procedures will be performed before administration of the in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Complete physical examination
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC
  - Immunology assessments
- Urine pregnancy test (for sexually active females of childbearing potential only)
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
  - FAQLQ and FAIM
  - FAQL-PB

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.3.5 Extended Maintenance Period (Visit Every 3 Months)

In the Extended Maintenance Period, clinic visits will occur every 3 months ±2 weeks (with the first visit designated as Month 3) until the end of treatment (early discontinuation or study completion).

The following procedures will be performed before administration of each in-clinic dose of AR101:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Physical examination
  - Complete physical examination with weight and height at 6-month intervals (Month 6, 12, 18, etc, visits) only;
  - Abbreviated physical examination at other visits
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (at annual visits [Months 12, 24, 36, etc] only)
  - Immunology assessments (at annual visits [Months 12, 24, 36, etc] only)
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT (at annual visits [Months 12, 24, 36, etc] only)
- Completion of questionnaires (at annual visits only):
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)
- Completion of questionnaires (at 6-month intervals [Month 6, 12, 18, etc, visits] only):
  - FAQLQ and FAIM
  - FAQL-PB

After completion of these procedures, for subjects not undergoing OLFC, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

After 12 months of treatment during Extended Maintenance and yearly thereafter, an OLFC will be conducted for subjects who have consented to this procedure (Appendix 10). AR101 will not be administered to these subjects on the day of their OLFC.

The following procedures will be performed before discharge from the clinic (regardless of completion of the OLFC):

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject or subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.3.6 End of Treatment Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of AR101 treatment, subjects will return to the clinic for the End of Treatment visit. A DBPCFC (Appendix 11) will be performed for all subjects except those who discontinue early for safety reasons. AR101 will not be administered on the days of the DBPCFC. AR101 dosing will continue until after last food challenge is performed.

The following procedures will be performed before the DBPCFC:

- Monitoring and recording of AEs, including allergic symptoms
- Concomitant medication review
- Food allergen exposure update
- Return of unused AR101
- AR101 dosing compliance check
- Complete physical examination, including weight and height
- Vital signs
- PEF (should be measured at approximately the same time of day at each visit assessment)
- Blood sample collection:
  - CBC (if not completed within prior 6 months)
  - Immunology assessments
- Urine pregnancy test (for sexually active females of childbearing potential only)
- SPT
- PEESS v2.0 (for subjects who had GI AEIs)
- Completion of questionnaires:
  - ACT/C-ACT (for subjects with known asthma only) (before PEF assessment)
  - TNSS (for subjects with known allergic rhinitis only)

- FAQLQ and FAIM
- FAQL-PB

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training

At the end of the End of Treatment visit, the investigator must advise the subject or parent/caregiver of appropriate options for continued management of peanut allergy.

Site staff will contact the subject or subject's parent/caregiver by telephone at least 14 days after the last AR101 dose or the last food challenge, whichever is last, to enquire if any AEs (including allergic symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic and to provide assistance in management of events.

7.3.7 Unscheduled Visit

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

The procedures performed at unscheduled visits may include any or all of those listed in Appendix 3.

7.3.8 Unscheduled Blood Sample

An unscheduled blood sample for CBC and immunologic assessments may be collected around the time of the last dose of AR101 during a scheduled or unscheduled visit for subjects who intend to discontinue dosing; a blood sample will not be required at the End of Treatment visit if this unscheduled blood sample is collected.

7.3.9 Follow-Up Observation Period

The End of Treatment visit will be followed by a 12-month observation period (Appendix 6). During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan
- Key events review

7.3.10 Study Exit Visit

The Study Exit visit will be conducted at 12 months after the last dose of AR101 (Appendix 6). An optional DBPCFC may be performed.

The following procedures will be performed:

- Verification of informed consent/assent for participation in the DBPCFC
- Height, weight
- Vital signs
- PEF
- Current treatment plan
- Key events review
- Abbreviated physical examination
- Blood sample collection for immunology assessments
- SPT
- FAQLQ and FAIM questionnaires

After completing these procedures, a DBPCFC will be performed for subjects who consent.

7.4 Treatment Pathway 4

7.4.1 Screening/Baseline Visit

Before any unique ARC008-related procedures are performed, the investigator or designee must obtain written informed consent/assent for this study from the subject and parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline visit occurs on the same day (+3 days) as the Exit visit of parent study ARC005, unless specified otherwise in the ARC005 protocol, and must be completed within 28 days after signed informed consent/assent is obtained.

Initiation of AR101 treatment in this study must be within 3 days after the ARC005 Exit visit for subjects treated with AR101 in study ARC005, unless specified otherwise in the ARC005 protocol. The first dose of AR101 in ARC008 should not be administered on the same day as an exit food challenge or dosing in study ARC005.

The following Screening/Baseline procedures will be conducted as part of ARC008 if not completed at the ARC005 Exit visit (or other visit if specified). A detailed list of Screening/Baseline procedures to be performed as part of ARC008 is provided as a guide in Appendix 4. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 4.

- Inclusion/exclusion criteria review
- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)

- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Demographics
- Medical and allergy history review
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon, evening])
- Asthma evaluation (for subjects with asthma only)
- EASI score (for subjects with eczema or atopic dermatitis only)
- Complete physical examination, including weight and height
- Concomitant medication review
- Food allergen exposure update
- Blood sample collection:
  - CBC
  - Immunology assessments
- SPT

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

- AE recording (including allergy symptoms)
- Peanut allergy training
- In-clinic dosing, unless the visit occurs on the same day as an exit food challenge or dosing in parent study ARC005
- AR101 dispensing
- Home dosing instruction (Section 5.2)
- Diary log dispensing

Site staff will contact the subject's parent/caregiver by telephone 6 to 7 weeks after the Screening/Baseline visit to enquire about compliance with AR101 dosing and if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.4.2 Extended Maintenance Period (Visits Every 3 Months)

During the Extended Maintenance Period, clinic visits will occur every 3 months ±2 weeks (with the first visit designated as Month 3) until the end of treatment (early discontinuation or study completion).

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver) (at annual visits only)

- C-ACT (for subjects aged ≥ 5 years with asthma only; complete before PEF) (at annual visits only)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- Physical examination (complete physical examination at 6-month intervals [Month 6, 12, 18, etc, visits] only; abbreviated physical examination at other visits)
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review (and dispensing of new diary log if needed)
- Return of unused AR101
- AR101 dosing compliance check
- Blood sample collection:
  - CBC (at annual visits [Months 12, 24, 36, etc] only)
  - Immunology assessments (at annual visits [Months 12, 24, 36, etc] only)
- SPT (at annual visits [Months 12, 24, 36, etc] only)

After completion of these procedures, for subjects not having an OLFC, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

An OLFC will be conducted after the first 12 months of treatment during Extended Maintenance. An optional OLFC will be conducted yearly thereafter for subjects whose parent/guardian consents to this procedure (Appendix 10). AR101 will not be administered to subjects on the day of the OLFC.

The following procedures will be performed before discharge from the clinic (regardless of completion of the OLFC):

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.4.3 End of Treatment Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of AR101 treatment, subjects will return to the clinic for the End of Treatment visit. A DBPCFC (Appendix 11) will be performed for all subjects except those who discontinue early for safety reasons. AR101 will not be administered on the days of the DBPCFC. AR101 dosing will continue until the last food challenge is performed.

The following procedures will be performed before the DBPCFC:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- EASI score (for subjects with eczema or atopic dermatitis only)
- Complete physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review
- Return of unused AR101
- AR101 dosing compliance check
- Blood sample collection:
  - CBC (if not completed within prior 6 months)
  - Immunology assessments
- SPT
- PEESS v2.0 (for subjects who had GI AEIs)

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training

At the end of the End of Treatment visit, the investigator must advise the parent/caregiver of appropriate options for continued management of peanut allergy.

Site staff will contact the subject's parent/caregiver by telephone at least 14 days after the last AR101 dose or last food challenge, whichever is last, to enquire if any AEs (including

allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic and to provide assistance in management of events.

7.4.4 Unscheduled Visit

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

The procedures performed at unscheduled visits may include any or all of those listed in Appendix 4.

7.4.5 Unscheduled Blood Sample

An unscheduled blood sample for CBC and immunologic assessments may be collected around the time of the last dose of AR101 during a scheduled or unscheduled visit for subjects who intend to discontinue dosing; a blood sample will not be required at the End of Treatment visit if this unscheduled blood sample is collected.

7.4.6 Follow-Up Observation Period

The End of Treatment visit will be followed by a 12-month observation period (Appendix 6). During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan
- Key events review

7.4.7 Study Exit Visit

The Study Exit visit will be conducted at 12 months after the last dose of AR101 (Appendix 6). An optional DBPCFC may be performed.

The following procedures will be performed:

- Verification of informed consent/assent for participation in the DBPCFC
- Height, weight
- Vital signs
- PEF (for subjects aged ≥ 4 years)
- Current treatment plan
- Key events review
- Abbreviated physical examination

- Blood sample collection for immunology assessments
- SPT

After completing these procedures, a DBPCFC will be performed for subjects who consent.

7.5 Treatment Pathway 5

7.5.1 Screening/Baseline Visit

Before any unique ARC008-related procedures are performed, the investigator or designee must obtain written informed consent/assent for this study from the subject and parent/guardian (as applicable), as described in Section 11.2. The Screening/Baseline visit must be completed within 28 days after signed informed consent/assent is obtained.

The following Screening/Baseline procedures will be conducted as part of ARC008 if not completed at the ARC005 Exit visit (or other visit if specified). A detailed list of Screening/Baseline procedures to be performed as part of ARC008 is provided as a guide in Appendix 5. Certain Screening/Baseline procedures must be repeated if last completed outside the windows specified in Appendix 5.

- Inclusion/exclusion criteria review
- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Demographics
- Medical and allergy history review
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment [eg, morning, afternoon, evening])
- Asthma evaluation (for subjects with asthma only)
- EASI score (for subjects with eczema or atopic dermatitis only)
- Complete physical examination, including weight and height
- AE recording (including allergy symptoms)
- Concomitant medication review
- Food allergen exposure update
- Blood sample collection:
  - CBC
  - Immunology assessments
- SPT

- Completion of questionnaires:
  - FAQLQ and FAIM
  - FAQL-PB
- Peanut allergy training

The site staff will schedule the Initial Escalation Period visits. Day 1 should occur within 10 days after the Screening/Baseline visit.

7.5.2 Initial Escalation Period

If the Initial Escalation Period is not started within 10 days after the Screening/Baseline visit, written approval to rescreen the subject and/or to waive any of the Screening/Baseline procedures must be obtained from a medical monitor.

7.5.2.1 Day 1

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), and suspected intercurrent illness before initiating dose escalation. Additionally, subjects must be fully recovered (ie, back to baseline state of health) from any preceding illness for at least 3 days, depending on the investigator's assessment of the severity of the illness.

Subjects may have clear liquids or flavored gelatin during the escalation procedure while the desensitization doses are administered.

The following procedures will be performed before dose escalation:

- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Complete physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.2.1.

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training

7.5.2.2 Day 2 (Day After Day 1)

Day 2 is the next consecutive day after Day 1, unless circumstances create a safety risk (eg, an intercurrent illness) for administering the next dose, consistent with the rules for missed doses (Section 5.4). If such a circumstance occurs, the investigator must discuss the case with a medical monitor before administering the next dose.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness before administration of the confirmatory dose.

The following procedures will be performed before the confirmatory dose of AR101 is administered:

- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Abbreviated physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.2.2.

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)
- Diary log dispensing

Site staff will contact the subject's parent/caregiver by telephone the next day (may be within 2 days if next day is not feasible) to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.3 Up-Dosing Period (Visits Every 2 Weeks for 24 to 40 Weeks)

During the Up-Dosing Period, the first dose at each new dose level will be administered in the clinic with visits every 2 weeks (±3 days) up to 40 weeks.

Unscheduled visits may be conducted for assessment of dose tolerability, dose reduction, or dose re-escalation or management of AEs.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness before a dose is administered in the clinic. Subjects should be maintained on the current or a reduced dose level of AR101 until the active wheezing, flare of atopic disease, or intercurrent illness has resolved.

Subjects should withhold their daily home dose of AR101 on days the dose is administered in the clinic but should take all other prescribed medications as scheduled.

The following guidelines for dose escalation and reduction will be followed during the Up-Dosing Period:

- A dose escalation attempt may be postponed 1 to 2 weeks if the current dose level has not been sufficiently tolerated to proceed to the next dose level per investigator judgement.
- Further, if an investigator suspects that a subject has not tolerated or is not tolerating the current dose level, the investigator should have the subject return to the clinic to determine whether a dose reduction is warranted. Guidelines for dose reduction are outlined in Section 6.8,with the dose adjustment depending on the severity of symptoms related to dosing.
- Subjects who require dose reduction during a 2-week period between visits will have the escalation schedule reset as necessary to maintain the new dose level for a 2-week period before attempting dose re-escalation.
- A dose re-escalation attempt should be made within 4 weeks after a dose reduction, unless dose escalation is to be delayed further because of administration of epinephrine (Section 6.10). Failure to successfully escalate the dose level after 3 consecutive attempts with at least 2 weeks between each escalation attempt will result in the discontinuation of dosing. The subject will have the End of Treatment visit (Section 7.5.6).

7.5.3.1 Up-Dosing Visits

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire, at 80 mg and 300 mg visits only (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT, at 80 mg and 300 mg visits only (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation, at 80 mg and 300 mg visits only (for subjects with asthma only)

- EASI score, at 80 mg and 300 mg visits only (for subjects with eczema or atopic dermatitis only)
- Physical examination (complete physical examination at 80 mg and 300 mg visits only; abbreviated physical examination at other visits)
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review (and dispensing of new diary log, if needed)
- Return of unused AR101
- AR101 dosing compliance check

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergic symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone the next day (may be within 2 days if next day is not feasible) to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.3.2 End Up-Dosing Visit

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- Abbreviated physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms

- Concomitant medication review
- Diary log review (and dispensing of new diary log, if needed)
- Return of unused AR101
- AR101 dosing compliance check
- Completion of questionnaires:
  - FAQLQ and FAIM
  - FAQL-PB

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 3.2.3.2 and Section 5.2. Subjects will be monitored as instructed in Section 5.3.3.

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone the next day (may be within 2 days if next day is not feasible) to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.4 Initial Maintenance Period (Visits Every 4 Weeks Until End of Initial Maintenance Visit)

During the Initial Maintenance Period, clinic visits will occur every 4 weeks ±3 days until the End of Initial Maintenance visit, when the subject completes an overall total of approximately 12 months of treatment (including initial dose escalation, up-dosing, and maintenance treatment).

Subjects should withhold their daily home dose of AR101 on days the dose is administered in the clinic but should take all other prescribed medications as scheduled.

The guidelines for dose escalation and reduction are the same as for the Up-Dosing Period (Section 7.5.3).

7.5.4.1 Initial Maintenance Visits

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- Abbreviated physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review (and dispensing of new diary log, if needed)
- Return of unused AR101
- AR101 dosing compliance check

After completion of these procedures, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone the next day (may be within 2 days if next day is not feasible) to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.4.2 End of Initial Maintenance Visit

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)

- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- Complete physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review (and dispensing of new diary log, if needed)
- Return of unused AR101
- AR101 dosing compliance check
- Blood sample collection (only for subjects who complete an overall total of approximately 12 months of treatment):
  - CBC
  - Immunology assessments
- SPT (only for subjects who complete an overall total of approximately 12 months of treatment)
- Completion of questionnaires:
  - FAQLQ and FAIM
  - FAQL-PB

An OLFC will be conducted after completion of these procedures and after an overall total of approximately 12 months of treatment (including initial dose escalation, up-dosing, and maintenance treatment). AR101 will not be administered to subjects on the day of the OLFC.

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.5 Extended Maintenance Period (Visits Every 3 Months)

During the Extended Maintenance Period, clinic visits will occur every 3 months ±2 weeks (with the first visit designated as Month 3) until the end of treatment (early discontinuation or study completion).

The following procedures will be performed before AR101 is administered in the clinic:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver) (at annual visits only)
- C-ACT (for subjects aged ≥ 5 years with asthma only; complete before PEF) (at annual visits only)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation (for subjects with asthma only)
- Physical examination (complete physical examination at 6-month intervals [Month 6, 12, 18, etc, visits] only; abbreviated physical examination at other visits)
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review (and dispensing of new diary log, if needed)
- Return of unused AR101
- AR101 dosing compliance check
- Blood sample collection:
  - CBC (at annual visits [Months 12, 24, 36, etc] only)
  - Immunology assessments (at annual visits [Months 12, 24, 36, etc] only)
- SPT (at annual visits [Months 12, 24, 36, etc] only)
- Completion of questionnaires (at 6-month intervals [Month 6, 12, 18, etc visits] only):
  - FAQLQ and FAIM
  - FAQL-PB

After completion of these procedures, for subjects not having an OLFC, AR101 will be administered in the clinic as instructed in Section 5.2. Subjects will be monitored as instructed in Section 5.3.4.

An OLFC will be conducted after the first 12 months of treatment during Extended Maintenance. An optional OLFC will be conducted yearly thereafter for subjects whose parent/guardian consents to this procedure (Appendix 10). AR101 will not be administered to these subjects on the day of the OLFC.

The following procedures will be performed before discharge from the clinic (regardless of completion of the OLFC):

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training
- AR101 dispensing
- Home dosing instruction (Section 5.2)

Site staff will contact the subject's parent/caregiver by telephone 6 to 7 weeks after this visit to monitor compliance with AR101 dosing, enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic, and to provide assistance in recording and management of events.

7.5.6 End of Treatment Visit

At the early discontinuation of AR101 dosing (for subjects who discontinue early) or at the end of AR101 treatment, subjects will return to the clinic for the End of Treatment visit. A DBPCFC (Appendix 11) will be performed for all subjects except those who discontinue early for safety reasons. AR101 will not be administered on the days of the DBPCFC. AR101 dosing will continue until the last food challenge is performed.

The following procedures will be performed before the DBPCFC:

- TRACK questionnaire (for subjects aged 1 to < 5 years with asthma only; completed by the parent/caregiver)
- C-ACT (for subjects aged ≥ 5 years with asthma only) (complete before PEF)
- Weight, height
- Vital signs
- PEF (for subjects aged ≥ 4 years) (should be measured at approximately the same time of day at each visit assessment)
- Asthma evaluation
- EASI score
- Complete physical examination
- Food allergen exposure update
- Monitoring and recording of AEs, including allergy symptoms
- Concomitant medication review
- Diary log review
- Return of unused AR101
- AR101 dosing compliance check
- Blood sample collection:
  - CBC (if not completed within prior 6 months)
  - Immunology assessments

- SPT
- Completion of questionnaires:
  - FAQLQ and FAIM
  - FAQL-PB
- PEESS v2.0 (for subjects who had GI AEIs)

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

- Monitoring and recording of AEs, including allergy symptoms
- Peanut allergy training

At the end of the End of Treatment visit, the investigator must advise the subject's parent/caregiver of appropriate options for continued management of peanut allergy.

Site staff will contact the subject's parent/caregiver by telephone at least 14 days after the last AR101 dose or last food challenge, whichever is last, to enquire if any AEs (including allergy symptoms, GI symptoms, and accidental/nonaccidental food allergen exposure) occurred after the subject left the clinic and to provide assistance in management of events.

7.5.7 Unscheduled Visit

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

The procedures performed at unscheduled visits may include any or all of those listed in Appendix 5.

7.5.8 Unscheduled Blood Sample

An unscheduled blood sample for CBC and immunologic assessments may be collected around the time of the last dose of AR101 during a scheduled or unscheduled visit for subjects who intend to discontinue dosing; a blood sample will not be required at the End of Treatment visit if this unscheduled blood sample is collected.

7.5.9 Follow-Up Observation Period

The End of Treatment visit will be followed by a 12-month observation period (Appendix 6). During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan
- Key events review

7.5.10 Study Exit Visit

The Study Exit visit will be conducted at 12 months after the last dose of AR101 (Appendix 6). An optional DBPCFC may be performed.

The following procedures will be performed:

- Verification of informed consent/assent for participation in the DBPCFC
- Height, weight
- Vital signs
- PEF (for subjects aged ≥ 4 years)
- Current treatment plan
- Key events review
- Abbreviated physical examination
- Blood sample collection for immunology assessments
- SPT
- FAQLQ and FAIM questionnaires

After completing these procedures, a DBPCFC will be performed for subjects who consent.

8 ADVERSE EVENTS AND SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

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

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

8.1.2 Adverse Reaction

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

An adverse reaction is any AE caused by the IP.

8.1.3 Serious Adverse Event

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

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

It is anticipated that the most likely cause of SAEs in this study will be anaphylaxis; however, not all occurrences of anaphylaxis are necessarily SAEs.

8.1.4 Adverse Event of Interest

AEIs include anaphylaxis, GI AEs with prolonged dose interruption (> 7 consecutive days) or that result in early discontinuation, accidental and nonaccidental food allergen exposure, severe adverse events, and use of epinephrine. Allergic reactions during food challenges will not be considered related to study product or reported as AEIs.

AEIs will be reported to the Safety Reporting Center within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study product.

8.1.4.1 Anaphylaxis

Anaphylaxis and systemic allergic reaction are synonymous terms in this study. In AR101 clinical program reporting (eg, in the AR101 investigator brochure), anaphylaxis refers only to *severe* systemic allergic reactions.

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

The clinical criteria for suspected anaphylaxis are defined in Appendix 7 and the severity grading parameters are provided in Appendix 8. When the diagnosis of anaphylaxis is made, the basis for suspecting the diagnosis must be documented using these criteria.

With respect to the inclusion of being potentially life-threatening in the definition of anaphylaxis and how that relates to the assessment of anaphylaxis as an SAE, reference is made to the Definitions and Standards for Expedited Reporting in the ICH E2A Tripartite Guideline, which states the following:

> An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Thus, for the reporting of anaphylaxis as an SAE, the severity of the reaction, assessed according to the European Academy of Allergy and Clinical Immunology (EAACI) system for grading the severity of anaphylactic reactions (Muraro, 2007), is also to be taken into account (Section 8.2.2.1 and Appendix 8).

8.1.4.2 Gastrointestinal AEs Resulting in Prolonged Interruption of Dosing

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

To delineate these AEIs, prolonged interruption of dosing is defined as withholding AR101 for > 7 days. This will include 3 categories of subjects:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus
- Any subject who experienced GI AEs and discontinues early from the study

Subjects with GI AEIs will be asked to complete the PEESS v2.0 questionnaire (Franciosi, 2011) while the subject is symptomatic, at the End of Treatment visit, and then monthly for 6 months thereafter. Parents/caregivers will also complete the PEESS v2.0 as appropriate. It should be noted that the PEESS v2.0 was not designed to establish a diagnosis of EoE; the use of the PEESS v2.0 to monitor the clinical course of GI symptoms must be

considered exploratory. However, the PEESS v2.0 has shown content and construct validity (Franciosi, 2011; Martin, 2015) and holds promise for being a valuable tool to follow the clinical course of EoE or an EoE-like immune-mediated GI syndrome. The PEESS v2.0 could reveal trends toward symptomatic improvement or worsening that might otherwise go undetected.

Subjects who discontinue AR101 treatment early due to chronic/recurrent GI AEs will be requested to return to the clinic for evaluation monthly for at least 6 months (if the subject is asymptomatic, telephone follow-up with a physician investigator may substitute for in-clinic visit, at the investigator's discretion). If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management.

If chronic/recurrent GI AEs do not completely resolve within 6 weeks after discontinuation of AR101 dosing, the subject should be referred to a (pediatric) gastroenterologist. Subjects with EoE confirmed by biopsy will have safety follow-up monthly for at least 6 months or until resolution of symptoms and/or tissue eosinophilia, whichever is last.

If a subject who discontinued AR101 treatment early due to chronic/recurrent GI AEs is unable to discontinue the use of symptomatic therapies initiated to treat the GI AEs (eg, H1 or H2 histamine blockers or proton pump inhibitors) by 12 weeks from the time that AR101 was discontinued, the subject should be referred to a (pediatric) gastroenterologist.

As is the case for any AE occurring during the study, for chronic/recurrent GI AEs, the investigator may use discretion anytime to request consultation from an outside physician or additional testing to assist in the diagnosis or management of the AE.

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

8.1.4.3 Accidental and Nonaccidental Food Allergen Exposures

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

Subjects will 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 nonserious AEI form will be completed for each of these events, in addition to events where consumption of peanut without a reaction occurs, *unless*:

- The accidental/nonaccidental food ingestion safety event meets the definition of an SAE as defined in Section 8.1.3, in which case the SAE form will be completed.

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

8.1.4.4 Severe Adverse Events

Any AE meeting the criteria for severe as defined in Section 8.2.2.1 will be reported as an AEI.

8.1.4.5 Adverse Events Associated With Use of Epinephrine

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

8.1.5 Unexpected Adverse Event

An AE is unexpected when its nature, severity, or specificity is not consistent with applicable product information such as safety information provided in the package insert, the investigational plan, the investigator brochure, or the protocol. The reference safety information for assessment of expectedness of serious adverse reactions to AR101 for reporting purposes is provided in the AR101 investigator brochure.

8.1.6 Clinically Significant Laboratory Results

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

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

8.2 Adverse Event Monitoring and Recording

8.2.1 Monitoring Procedures

All AEs will be recorded from the time of signing of the ICF through at least 14 days after the last AR101 dose, 14 days after the last food challenge, or until resolution or stabilization of all AEs ongoing at the time dosing is stopped, whichever is later. In the event the ICF for

ARC008 is signed before the prior study exit visit, AEs will be recorded from the time of the Screening/Baseline visit.

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

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

AEs may be discovered through any of the following methods:

- Observing the subject
- Questioning the subject, which should be done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records/medical notes

8.2.2 Recording Procedures

All AEs will be recorded in the source documents from the time of signing of the ICF through at least 14 days after the last AR101 dose or last food challenge, whichever is last. In the event the ICF for ARC008 is signed before the prior study exit visit, AEs will be recorded from the time of the Screening/Baseline visit. Recording of these AEs into the eCRF is described in the eCRF completion guidelines.

Any event that meets the definition of an SAE (Section 8.1.3) will also be reported to the study Safety Reporting Center using an SAE report form as described in Section 8.3 in addition to completing the AE form. SAE follow-up reports should include, as applicable, hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment, and any other pertinent information regarding the event. Reporting should not be delayed in order to provide these documents. In the event of a death, other supporting data (death certificate, medical notes, etc) should be included. Source documents, with subject identifiers redacted, can be scanned and attached to the AE form as well.

AE Type	Form	Reference Section
All AEs	eCRF	8.2.1-8.2.2
SAE	SAE Form	8.1.3
AEI	AEI Form	8.1.4.1-8.1.4.5
Pregnancy	Pregnancy Form	8.1.1

AE = adverse event; AEI = adverse event of interest; eCRF = electronic case report form; SAE = serious adverse event.

8.2.2.1 Assessment of Severity

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

- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 8).
- The severity of allergic reactions will be graded according to the definitions developed by the CoFAR group (Appendix 9).
- The severity of all other AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) system. The purpose of using the NCI-CTCAE system is to provide standard language to describe AEs ("toxicities") and to facilitate tabulation and analysis of the data and for assessment of the clinical significance of treatment-related toxicities. The NCI-CTCAE provides a term and a grade that closely describes the AE. Each participating site will receive copies of the grading scales and event descriptions. For additional information and a printable version of the NCI-CTCAE v.4.03 manual, consult the NCI-CTCAE website, http://ctep.cancer.gov/reporting/ctc.html.
- AEs not included in the NCI-CTCAE listing will also to be graded on a scale from 1 to 5, according to these general grade definitions:
  - **Grade 1 (Mild):** Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (nonprescription or single-use prescription therapy may be employed to relieve symptoms (eg, aspirin for simple headache, acetaminophen for postsurgical pain)
  - **Grade 2 (Moderate):** Mild to moderate limitation in activity, some assistance may be needed, no or minimal intervention/therapy required, hospitalization possible
  - **Grade 3 (Severe):** Marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalization possible
  - **Grade 4 (Life-threatening):** Extreme limitation in activity, significant assistance required, significant medical/therapy intervention required, hospitalization or hospice care probable
  - **Grade 5 (Death)**

8.2.2.2 Assessment of Causality (Relatedness)

The investigator will use the following criteria when assessing causality of an AE to AR101:

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

AE = adverse event.

8.3 Serious Adverse Event Reporting Procedures

All SAEs will be reported to the sponsor from the time of signing of the ICF through at least 14 days after the last AR101 dose or last food challenge, whichever is last. SAEs will be recorded in the electronic data capture (EDC) system. The site will also report an SAE to the Safety Reporting Center within 24 hours of the site's knowledge of the event using an SAE report form.

If the ICF for ARC008 is signed before the prior study exit visit, SAEs will be reported in the prior study until the time of the Screening/Baseline visit in ARC008. Thereafter, SAEs will be reported in ARC008.

If the investigator becomes aware of an SAE with a suspected causal relationship to AR101 that occurs within 30 days after the last AR101 dose, the investigator will report it to the sponsor.

The following attributes will be included in an SAE report:

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

The investigator will apply clinical judgment to determine whether an AE is of sufficient severity to require discontinuation of AR101. If necessary, an investigator will suspend any study procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

Subsequent review by regulatory authorities, the sponsor's internal safety risk management team, IRBs/ECs, or the sponsor may suspend further study treatment or procedures at a site. The study sponsor and the regulatory authorities retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Allergic reactions during food challenges that meet the criteria for serious will be reported as related to the procedure.

8.4 Serious Adverse Event Notification

8.4.1 Notifying the Sponsor

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

8.4.2 Expedited SAE Reporting to Health Authorities and Internal Safety Risk Management Team

The reference safety information for assessment of expectedness of serious adverse reactions to AR101 for reporting purposes is provided in the AR101 investigator brochure.

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

The sponsor will expedite the reporting to all concerned investigator(s), IRBs/ECs, where required, and to the national regulatory authorities of all suspected unexpected serious adverse 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 Safety Reporting Center will provide these expedited reports to each investigator. SAEs that are considered related to AR101 and are unexpected will be reported to regulatory authorities within 15 days or for deaths and life-threatening events within 7 days (in accordance with applicable regulatory reporting requirements).

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

Once a year throughout the clinical study, the sponsor will provide a listing of all SUSARs that occurred during this period and a safety report to the EC and health authorities of countries in whose territory the clinical study is conducted.

8.4.3 Notifying the Internal Safety Risk Management Team

The Safety Reporting Center will provide the sponsor's internal team (described in Section 3.3) with listings of all SAEs on an ongoing basis. Furthermore, the team will be informed of expedited SAE reports. The team will send periodic reports on the overall safety of the ongoing study and recommendations regarding continuation, and investigators will forward to the IRBs/ECs if required.

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

- An ER visit
- Hospitalization

- More than 2 doses of epinephrine being given as treatment for the same episode
- Assessment of the anaphylaxis as severe, as defined in Appendix 8. An initial Anaphylaxis Episode form containing the information known to the site at the time will be transmitted to the Safety Reporting Center. The Safety Reporting Center will then relay to the sponsor and team the individual anaphylaxis reports as they are obtained. The site will supplement the initial Anaphylaxis Episode report with additional information pertaining to an event as it becomes available and will forward the information to the Safety Reporting Center.

8.4.4 Notifying the Institutional Review Boards and Ethics Committees

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

8.5 Study Discontinuation

The sponsor reserves the right to terminate the study anytime for any reason. Regulatory authorities and IRBs/ECs will be notified in the event of study termination.

9 STATISTICAL CONSIDERATIONS

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

The statistical methods and SAP may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

9.1 Sample Size

There is no sample size calculation for this study. The sample size will be determined by the number of eligible subjects from each of the prior AR101 studies who participate in this study.

9.2 Analysis Conventions

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

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

Data will be listed for each subject.

9.3 Analysis Populations

The primary population for all analyses will be the safety population, which will consist of all subjects who receive AR101 during ARC008.

9.4 Interim Analysis

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

9.5 Subject and Demographic Data

9.5.1 Study Disposition

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

9.5.2 Baseline Characteristics and Demographics

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

9.5.3 Use of Medications

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

9.6 Efficacy Analyses

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

9.7 Safety Analyses

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

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

10 STUDY DATA

10.1 Electronic Data Capture System

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

Access to the EDC system will be password controlled.

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

10.2 Access to Data

The study sites will periodically permit authorized representatives of the study sponsor or regulatory authorities to examine clinical records and other medical notes for the purpose of safety monitoring, quality assurance review, audit, or evaluation of the study progress throughout the entire study period. The investigator is required by law and applicable guideline (21 CFR 312.62, EU Clinical Trials Directive 2001/20/EC, and ICH GCP) to keep accurate case records for at least 2 years after acceptance of a licensure application and record observations to assure the safe conduct of the study, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities are notified, or longer if required by local regulations.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Statement of Compliance

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

11.2 Informed Consent and Assent

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

The subject and/or parent/guardian will be allowed as much time as needed to review the document(s) and consider participation in the study. The investigator will review the consent/assent, answer any questions, and emphasize the need to avoid allergen exposure other than AR101 and the necessity to continue AR101 dosing to maintain desensitization. The prospective subject and/or pediatric subject's parent/guardian will be told that being in the study is voluntary and that the subject may withdraw from the study anytime and for any reason. Adult subjects and parents/guardians of pediatric subjects will each sign the ICF, and pediatric subjects will each sign the assent form, as required by the IRB/EC. Where required by local authorities, both parents must sign the consent form before a child can be enrolled in the study. The subject or subject's parent/guardian must be given a copy of the signed and dated ICF and assent form, if used. Written informed consent and assent must be obtained before any study-related procedure is performed.

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

Informed consent and assent procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

11.3 Privacy and Confidentiality

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

11.4 Study Monitoring

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

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

Study monitoring may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 12.

11.5 Data Management

Quality control procedures and a feedback system between the data center and the sites will be instituted to ensure the accuracy and completeness of the data collected.

12 RESOURCE SHARING

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

13 PROTOCOL DEVIATIONS

The investigators and study site staff will conduct the study in accordance with the protocol. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Whenever applicable, protocol deviations will result in development of corrective and preventive actions by the site and prompt implementation.

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

Protocol deviations must be clearly documented, including the reasons for the deviations. The principal investigator is responsible for reporting protocol deviations in accordance with their local IRBs/IECs requirements.

13.1 Reporting and Managing Protocol Deviations

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

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

14 BIOLOGICAL SAMPLES

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

15 FINANCING AND INSURANCE

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

16 REFERENCE LIST

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