CLINICAL STUDY PROTOCOL

ARC009

Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adolescents: Real-World, Open-Label, Quality of Life Study

Protocol Amendment 1.0 – 11 Apr 2018

Reference Numbers: NCT03703791, EudraCT 2018-000326-58

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Aimmune Therapeutics, Inc.

CLINICAL STUDY PROTOCOL

Protocol Title:	Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adolescents: Real-World, Open-Label, Quality of Life Study
Protocol Identifier:	ARC009
Phase:	3b
Investigational Product:	AR101
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Blvd, Suite 300 Brisbane, CA 94005 United States
Reference Number:	EudraCT 2018-000326-58
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Original Protocol:	0.0 – 03 Apr 2018
Amendments	
Global:	1.0 – 11 Apr 2018

This study will be conducted according to the Declaration of Helsinki (2013), principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents, EU Directive 2001/20/EC (the Clinical Trials Regulation), EU Directive 2005/28/EC (Good Clinical Practice Directive), and local applicable legislation including but not limited to the UK SI 2004/1031 Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

SYNOPSIS

Title of Study: Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adolescents: Real-World, Open-Label, Quality of Life Study

Short Title: AR101 Health-Related Quality of Life (HRQOL) Study in Peanut-Allergic Subjects

Protocol Identifier: ARC009

EudraCT: 2018-000326-58

Phase of Development: 3b

Number of Subjects: Approximately 200

Study Centers: Approximately 45 in Europe

Purpose of the Study: To compare the HRQOL of AR101 characterized oral desensitization immunotherapy (CODIT™) in combination with standard of care (peanut avoidance, education) versus standard of care alone in peanut-allergic subjects aged 4 to 17 years, inclusive. The HRQOL of parents/caregivers will also be assessed.

Study Objectives:

Primary:

- To assess proxy- and self-reported disease-specific HRQOL of peanut-allergic subjects aged 4 to 17 years, inclusive, receiving AR101 in combination with standard of care versus standard of care alone for approximately 18 months

Secondary:

- Safety and tolerability of AR101

To characterize changes over the course of the study in the following:

- Disease-specific HRQOL of parents/caregivers
- Relationship between clinical efficacy of AR101 (change in level of sensitization to peanut allergen) and HRQOL of subjects and parents/caregivers

Exploratory:

To assess the following:

- Self-reported assessments of control and confidence; reassurance, worry, and severity of allergic reactions based on food challenge outcomes; and overall HRQOL
- Changes in nondisease-specific measures of HRQOL, anxiety, and depression in subjects and parents/caregivers
- Health state utility estimates for economic analysis
- Changes in peanut skin prick test (SPT) mean wheal diameters associated with AR101 treatment
- Changes in control of pre-existing concomitant atopic disease (asthma, allergic rhinitis, atopic dermatitis)
- Relationship between basophil activation, clinical efficacy of AR101, and changes in HRQOL
- AR101 treatment experience among subjects and parents/caregivers

Study Design:

This is a phase 3b, randomized, open-label, European study of the HRQOL of AR101 in combination with standard of care (AR101 herein) compared with standard of care alone in approximately 200 peanut-allergic subjects aged 4 to 17 years, inclusive. Standard of care includes avoidance of peanuts/peanut-containing foods, and education on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors). HRQOL of parents/caregivers will also be assessed. The safety and tolerability of AR101 will be evaluated.

Eligible subjects will be randomly assigned 2:1 to AR101 treatment or standard of care alone. Randomization will be stratified by age group (4-12 years and 13-17 years). Subjects in both treatment

groups and their parents/caregivers will have disease-specific and nondisease-specific HRQOL assessments at screening and periodically thereafter.

Subjects receiving AR101 treatment will have 3 consecutive AR101 dosing periods before exiting (completing) the study: initial dose escalation, up-dosing, and maintenance. Subjects receiving standard of care alone will have approximately 18 months of observation before exiting (completing) the study. Subjects in both treatment groups will have a graded open-label food challenge (OLFC) up to a maximum single highest dose of 1000 mg of peanut protein (2043 mg cumulative), approximately 12 months after randomization.

AR101 Treatment Group

Initial dose escalation: Subjects randomly assigned to AR101 treatment will begin with a stepwise dose escalation of AR101 (up to 5 single doses of 0.5, 1, 1.5, 3, and 6 mg) administered at 20- to 30-minute intervals as tolerated at the study site.

- Subjects who tolerate at least 3 mg of AR101 on day 1 will return to the study site on day 2 to receive a single confirmatory 3 mg dose under direct observation. Subjects who tolerate the 3 mg confirmatory dose with no or mild symptoms that are not dose-limiting will begin the up-dosing period.
- Subjects who do not tolerate at least 3 mg of AR101 on day 1 or day 2 will stop AR101 treatment and discontinue early from the study.

Up-dosing: The up-dosing period will be approximately 6 months (22-40 weeks). Dose escalation will occur approximately every 2 weeks. Daily AR101 doses during up-dosing will be 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of AR101 at each new dose level will be administered under direct observation at the study site; the remaining doses at each dose level will be administered daily at home as tolerated. Subjects able to tolerate 300 mg for 2 weeks will begin the maintenance period. Subjects unable to tolerate 300 mg/day for 2 weeks within 40 weeks of up-dosing will stop AR101 treatment and discontinue early from the study.

Maintenance: Subjects will continue AR101 daily dosing at 300 mg/day for an additional 12 months (52 weeks) with study site visits every 4 weeks. After at least 6 months (up to 7 months) of maintenance treatment (approximately 12 months after randomization/first dose of AR101), subjects will have a graded OLFC up to a maximum single highest dose of 1000 mg of peanut protein (3, 10, 30, 100, 300, 600, 1000 mg [2043 mg cumulative]).

- Subjects who tolerate 1000 mg of peanut protein (2043 mg cumulative) at the OLFC will continue AR101 daily at 300 mg/day and will have the option to consent for a real-world peanut challenge (RWPC) within 4 weeks (preferably within 1 week) after the OLFC. During the RWPC, subjects will eat a food containing 500 to 600 mg of peanut protein under direct observation at the study site. Subjects who complete the RWPC (regardless of the outcome) will continue daily maintenance treatment with AR101 at 300 mg/day for a total of 52 weeks of maintenance until study exit.
- Subjects who tolerate at least 300 mg but < 1000 mg of peanut protein (2043 mg cumulative) at the OLFC or tolerate 1000 mg of peanut protein (2043 mg cumulative) but do not consent to the optional RWPC will continue daily maintenance treatment with AR101 at 300 mg/day for a total of 52 weeks of maintenance until study exit.
- Subjects who do not tolerate at least 300 mg of peanut protein at the OLFC will stop AR101 treatment and discontinue early from the study.

Standard of Care Treatment Group

Subjects receiving standard of care alone will have approximately 18 months of observation before study exit, with an OLFC approximately 12 months after randomization. Subjects receiving standard of care alone who complete the OLFC will not have an RWPC.

Both Treatment Groups

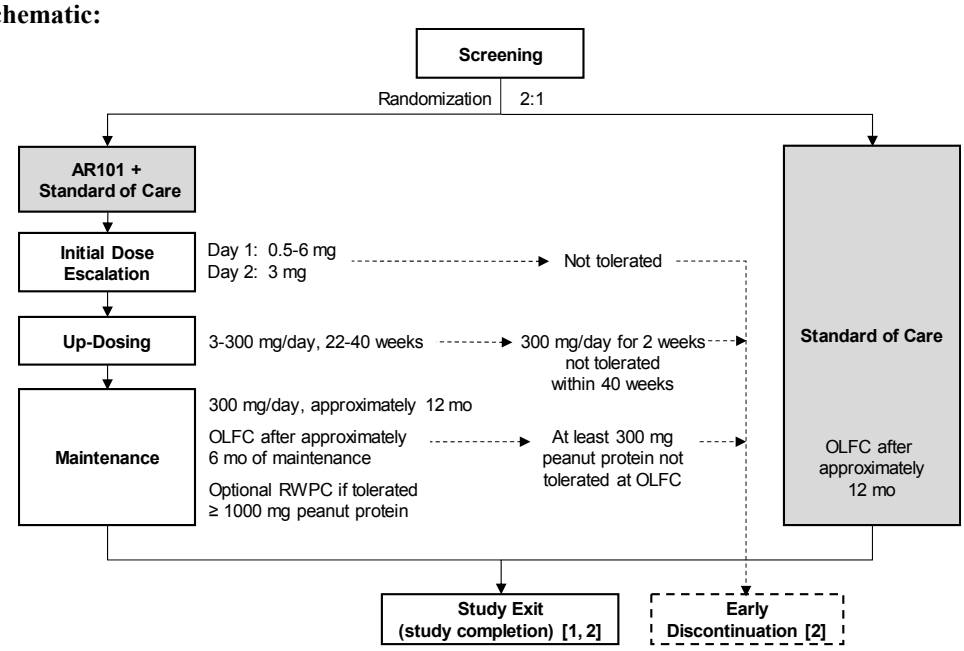
Early discontinuation: Subjects with unresolved adverse events at early discontinuation or who had gastrointestinal (GI) adverse events of interest will have safety follow-up.

Subjects who discontinue AR101 treatment early before completing 9 months of maintenance, and their parents/caregivers, will complete relevant follow-up HRQOL questionnaires.

Study exit: Subjects with unresolved adverse events at study exit or who had GI adverse events of interest will have safety follow-up. AR101-treated subjects who complete approximately 12 months of maintenance

treatment at 300 mg/day will have the option to enroll in an open-label follow-on study to continue AR101 treatment until it becomes commercially available or its development is terminated. Subjects who receive standard of care alone and complete approximately 18 months of observation will also have the option to receive AR101 treatment in a follow-on study. Subjects may continue to receive AR101 maintenance treatment or standard of care alone in ARC009 if the open-label follow-on study is not activated at their study site when subjects complete their course of treatment/observation.

Study Schematic:



AR101 + standard of care: Scheduled visits are day 1, day 2, every 2 weeks during up-dosing (22-40 weeks, approximately 6 months), and every 4 weeks during maintenance (52 weeks, approximately 12 months) until study exit (completion), with an OLFC after approximately 6 months of maintenance and RWPC (if applicable) within 4 weeks (preferably within 1 week) after the OLFC. Questionnaires are completed before randomization and approximately every 3 months thereafter.

Standard of care: Scheduled visits are approximately every 3 months for approximately 18 months until study exit (completion), with an OLFC approximately 12 months after randomization. Questionnaires are completed before randomization and approximately every 3 months thereafter.

[1] Subjects will have the option to receive AR101 in an open-label follow-on study.

[2] Subjects with unresolved adverse events at early discontinuation or study exit or who had GI adverse events of interest will have safety follow-up. Subjects who discontinue AR101 treatment early before completing 9 months of maintenance and their parents/caregivers will complete relevant follow-up HRQOL questionnaires.

GI, gastrointestinal; HRQOL, health-related quality of life; mo, months; OLFC, open-label food challenge; RWPC, real-world peanut challenge.

Key Eligibility Criteria:

Subjects must be aged 4 to 17 years, inclusive, at screening; have a history of physician-diagnosed immunoglobulin (Ig) E-mediated peanut allergy; have a mean wheal diameter on SPT to peanut ≥ 8 mm greater than the negative saline control at screening; and serum IgE to peanut of ≥ 14 kUA/L at screening. Written informed consent and assent (as appropriate) is required. Subjects must not have a history of severe or life-threatening anaphylaxis or anaphylactic shock within 60 days before screening; history of eosinophilic esophagitis (EoE) or other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia, or recurrent GI symptoms of any etiology; history of a mast cell disorder (eg, systemic mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism [eg, cold urticaria, cholinergic urticaria], or hereditary or idiopathic angioedema); have severe persistent asthma or mild or moderate asthma that is uncontrolled or difficult to control; history of high-dose corticosteroid medication use (eg, > 3 days at 1-2 mg/kg of prednisone or equivalent); or history of cardiovascular disease (including uncontrolled or inadequately controlled

hypertension). A palatable vehicle food to which the subject is not allergic must be available for administering AR101.

Test Product, Dose, and Mode of Administration:

AR101 consists of peanut flour characterized for quantities of specific peanut allergens and is formulated with bulking and flow agents in graduated doses. AR101 will be provided in pull-apart capsules containing 0.5, 1, 10, 20, or 100 mg of peanut protein. AR101 will also be provided as 300 mg of peanut protein in foil-laminate sachets for use during the maintenance period. Capsules/sachets will be opened; the contents delivered over an age-appropriate, semisolid, vehicle food; and mixed thoroughly.

The sponsor will supply the AR101 for this study. Trained study site personnel will dispense AR101 to the subject or parent/caregiver as appropriate for the assigned dose level.

Reference Therapy, Dose, and Mode of Administration:

Standard of care, including avoidance of peanuts/peanut-containing foods, and education on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors).

Duration of Treatment:

The total duration of treatment (AR101 treatment or standard of care alone) is approximately 18 months for each subject.

The total duration of the study is approximately 30 months (subject to delays during up-dosing or food challenges), assuming an approximate 6-month enrollment period and 24 months between the first subject screened and the last assessment for the last subject.

The end of the study is defined as the last assessment for the last subject in the study.

Quality of Life:

The following instruments will be used to assess the HRQOL objectives and are to be completed in the order given as required:

Summary of Instruments for Subject- and Parent/Caregiver-Reported HRQOL and Other Outcomes

Questionnaires/Bespoke Questions	Individual Assessed	Completed by
EQ-5D-5L	Parent/caregiver and subject aged 13-17 years	Parent/caregiver and subject
FAQL-PB	Parent/caregiver	Parent/caregiver
HADS	Parent/caregiver	Parent/caregiver
EQ-5D-Y proxy version	Subject aged 4-7 years	Parent/caregiver
EQ-5D-Y	Subject aged 8-12 years	Subject
FAQLQ-PF and FAIM-PF	Subject aged ≤ 12 years	Parent/caregiver
FAQLQ-PFT and FAIM-PFT	Subject aged 13-17 years	Parent/caregiver
FAQLQ-CF and FAIM-CF	Subject aged 8-12 years	Subject
FAQLQ-TF and FAIM-TF	Subject aged 13-17 years	Subject
Bespoke global assessment of HRQOL		
Parent/caregiver form	Subject	Parent/caregiver
Teenager form	Subject aged ≥ 13 years	Subject
Child form	Subject aged 8-12 years	Subject
Bespoke assessment of control and confidence		
Parent/caregiver form	Parent/caregiver	Parent/caregiver
Teenager form	Subject aged ≥ 13 years	Subject
Bespoke assessment of food challenge outcomes		
Parent/caregiver form	Parent/caregiver	Parent/caregiver
Patient form	Subject aged ≥ 13 years	Subject
TSQM-9	AR101-treated subject	Subject aged ≥ 13 years and parent/caregiver of subject aged 4-12 years
Bespoke exit questionnaire		
Parent/caregiver form	Parent/caregiver of AR101-treated subject	Parent/caregiver

Patient form	AR101-treated subject aged ≥ 13 years	Subject
Qualitative exit interview [1]	Parent/caregiver of AR101-treated subject and AR101-treated subject aged ≥ 13 years at study exit or early discontinuation	Parent/caregiver and subject

The same parent/caregiver should complete all relevant questionnaires during the study. For age-relevant questionnaires, a subject who transitions from one age group to the next age group during the study will complete the version first used.

[1] To be conducted in a random sample of parents/caregivers and subjects aged ≥ 13 years at study exit or early discontinuation.

EQ-5D, European Quality of Life 5-Dimensions health questionnaire; EQ-5D-5L, EQ-5D 5-Levels; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; TSQM-9, Treatment Satisfaction Questionnaire for Medication.

Statistical Methods:

The statistical methods and data presentations for reporting the study results will be described in detail in the statistical analysis plan. No interim analyses are planned.

Randomization will be central and treatment allocation will be 2:1 (AR101 treatment or standard of care alone). Randomization will be stratified by age group (4-12 years and 13-17 years).

HRQOL Analyses:

All HRQOL analyses will be performed using the intent-to-treat (ITT) population unless otherwise specified. The ITT population will be defined as all subjects who receive any part of 1 dose of study product and complete 1 study visit if assigned to AR101 treatment, or who complete 1 study visit after the screening visit if assigned to standard of care alone. The ITT population will be analyzed according to randomized treatment.

No single endpoint is specified as primary because the study is not designed or intended to support a labelling claim. The primary analysis will be on a family of proxy- and self-reported disease-specific HRQOL measures that assess HRQOL of the peanut-allergic subject (FAQLQ-PF, FAQLQ-PFT, FAQLQ-CF, FAQLQ-TF, FAIM-PF, FAIM-PFT, FAIM-CF, and FAIM-TF). Data summaries will be presented across time and accompanied by inferential analyses. Data will also be summarized separately by age group as appropriate for the questionnaire evaluated.

Analysis of Other Questionnaires:

Details of the analyses for other questionnaires (EQ-5D, FAQL-PB, HADS, and TSQM-9) and bespoke questions (global assessment of HRQOL, assessment of control of peanut allergy and confidence in managing allergic reactions, assessment of experiences related to food challenges, and assessment of experience and satisfaction with AR101 treatment at study exit) will be presented in the statistical analysis plan.

Efficacy Analyses:

All efficacy analyses will be performed using the ITT population unless otherwise specified. Subjects will be analyzed according to randomized treatment.

The proportion of subjects tolerating a single dose of 300 mg (443 mg cumulative), 600 mg (1043 mg cumulative), and 1000 mg (2043 mg cumulative) of peanut protein with no or mild symptoms in the OLFC after approximately 12 months of study treatment will be compared between treatment groups using the Fisher exact test. Desensitization response rates and associated 95% CIs will be presented for each treatment group using exact Clopper-Pearson CIs.

Additional efficacy endpoints include the following:

- The maximum dose reached with no or mild symptoms at the OLFC, assessed by tabulating the number and percentage of subjects by maximum dose at the OLFC and by treatment group

- The maximum severity of symptoms occurring at each challenge dose of peanut protein during the OLFC, assessed by tabulating the number and percentage of subjects by maximum severity at the OLFC and by treatment group
- The proportion of subjects successfully completing the RWPC with no or mild symptoms after approximately 13 months of AR101 treatment, assessed by presenting the response rate and associated 95% CI using an exact Clopper-Pearson CI
- The maximum severity of symptoms during the RWPC after approximately 13 months of AR101 treatment in eligible subjects who consented to the RWPC, assessed by tabulating the number and percentage of subjects by maximum severity

Safety Analyses:

All safety analyses will be performed using the safety population, defined as all subjects who receive any randomized study treatment. Safety data will be listed and summarized by treatment received. Descriptive statistics will be used.

Safety data will be collected from signed informed consent/assent through early discontinuation or study exit, and through at least 30 days after early discontinuation or study exit for subjects with unresolved adverse events or through at least 6 months after early discontinuation or study exit for subjects with GI adverse events of interest. Adverse events will be classified by system organ class and coded to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be classified by severity using the Consortium of Food Allergy Research (CoFAR) grading system for allergic reactions, European Academy of Allergy and Clinical Immunology (EAACI) guidelines for anaphylaxis, and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for all other adverse events.

The safety of AR101 treatment versus standard of care alone will be evaluated by the analysis of the incidence of nonserious and serious adverse events, severity of adverse events, incidence and severity of treatment-related adverse events, incidence of dose modifications (AR101 treatment only), and incidence of early treatment discontinuation due to adverse events and due to chronic or recurrent GI adverse events. Separate summaries will be presented for anaphylaxis, allergic reaction adverse events, use of epinephrine, and accidental and nonaccidental food allergen exposure. Summary statistics will be provided for the Asthma Control Test (ACT), lung function data, and laboratory data if relevant.

Other Analyses:

Additional endpoints to be assessed over the course of the study include the following:

- Changes from baseline in Total Nasal Symptom Score (TNSS) scores in subjects with pre-existing allergic rhinitis
- Changes from baseline in scoring atopic dermatitis (SCORAD) scores in subjects with pre-existing atopic dermatitis
- Changes in peanut SPT mean wheal diameters

Sample Size Considerations:

This study will use multiple HRQOL questionnaires to assess changes across time in the HRQOL of subjects receiving AR101 treatment versus standard of care alone and their parents/caregivers.

The sample size for this study is based on estimates for the FAQLQ-PF. A sample size of 144 subjects randomly assigned in a ratio of 2:1 to AR101 treatment (96 subjects) or standard of care alone (48 subjects) provides at least 80% power to detect a treatment difference of 0.75 in the adjusted mean total FAQLQ-PF scores at 18 months. The sample size calculation is based on an alpha of 0.05 and tests are assumed to be 2-sided. The common standard deviation is assumed to be 1.5. Approximately 25% of subjects are estimated to drop out or discontinue early from the study. Therefore, approximately 200 subjects (134, AR101 treatment; 67, standard of care alone) will be randomly assigned to study treatment.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Asthma Control Test
C-ACT	Childhood Asthma Control Test
CFR	Code of Federal Regulations
CODIT™	Characterized oral desensitization immunotherapy
CoFAR	Consortium of Food Allergy Research
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EC	Ethics committee (global term including institutional review boards, independent ethics committees, research ethics committees, and the like)
EoE	Eosinophilic esophagitis
EQ-5D	European Quality of Life 5-Dimensions health questionnaire
EQ-5D-5L	EQ-5D 5-Levels
EQ-5D-Y	EQ-5D Youth
FAIM	Food Allergy Independent Measure
FAIM-CF	FAIM - child form
FAIM-PF	FAIM - parent form
FAIM-PFT	FAIM - parent form teenager
FAIM-TF	FAIM - teenager form
FAQL-PB	Food Allergy Quality of Life – Parental Burden
FAQLQ	Food Allergy Quality of Life Questionnaire
FAQLQ-CF	FAQLQ - child form
FAQLQ-PF	FAQLQ - parent form
FAQLQ-PFT	FAQLQ - parent form teenager
FAQLQ-TF	FAQLQ - teenager form
FEV_1	Forced expiratory volume in the first second of expiration
GCP	Good Clinical Practice
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-related quality of life
ICH	International Council for Harmonisation
ID	Identification
Ig	Immunoglobulin
ITT	Intent-to-treat
IV	Intravenous
NHLBI	National Heart, Lung, and Blood Institute
OIT	Oral immunotherapy
OLFC	Open-label food challenge
PEESS v2.0	Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0
PEFR	Peak expiratory flow rate
RWPC	Real-world peanut challenge
SCORAD	Scoring atopic dermatitis
SPT	Skin prick test

Abbreviation	Definition
TNSS	Total Nasal Symptom Score
TSQM-9	Treatment Satisfaction Questionnaire for Medication
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Background

Peanut allergy is a common and serious condition that disproportionately affects children and is associated with severe reactions, including life-threatening anaphylaxis. The prevalence of peanut allergy has been rising in the Western world and is estimated to be approximately 2% to 3% in children (Turner, 2017); the cumulative incidence of childhood peanut allergy in the United Kingdom is approximately 0.7% (Grimshaw, 2016). The current standard of care for the management of peanut allergy is peanut avoidance, and education of the patient and family on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors).

Despite efforts at strict peanut avoidance, accidental exposure remains a major concern because allergic responses may be triggered by minute quantities (milligrams) of peanut protein. Strict adherence to an avoidance diet can be complicated by difficulty in interpreting food labels (Joshi, 2002), the presence of undeclared or hidden allergens in commercially prepared foods (Vierk, 2002; Altschul, 2001), and inattention to or mistrust of food warning labels (Vierk, 2007). Foods prepared outside the home (eg, at school, daycare centers, restaurants, homes of family/friends) present additional sources of accidental exposure. Accidental food allergen exposures are common, with 55% of peanut-allergic patients experiencing at least 1 allergic reaction over approximately 5 years (Sicherer, 1998). The burden of avoidance and constant fear of accidental exposure can negatively affect the health-related quality of life (HRQOL) for patients with peanut allergy and their families (Anagnostou, 2014; Avery, 2003; Primeau, 2000).

Early clinical studies of peanut oral immunotherapy (OIT) demonstrated promising safety and efficacy of this approach in peanut-allergic patients (Anagnostou, 2014; Yu, 2012; Varshney, 2011; Blumchen, 2010; Hofmann, 2009; Jones, 2009). Each of these studies included an oral food challenge to evaluate desensitization after completion of a period of dosing with increasing amounts of peanut flour, peanut protein, or whole crushed roasted peanuts, followed by a period of maintenance therapy, and showed that peanut OIT was generally well tolerated and could induce a clinically meaningful level of desensitization. Symptoms associated with peanut OIT 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. Additionally, studies suggest peanut OIT may induce favorable immunologic changes over time (Wambre, 2017; Kim, 2011; Varshney, 2011; Blumchen, 2010; Jones, 2009). The results of these studies and other experience with OIT in peanut and other common food allergies (Beyer, 2012; Burks, 2012; Keet, 2012) provided the rationale for initial clinical development of AR101 characterized oral desensitization immunotherapy (CODIT™) for subjects with peanut allergy.

AR101 consists of peanut flour characterized for quantities of specific allergenic peanut proteins, and is formulated with bulking and flow agents in graduated doses. The goal of continuous treatment with AR101 is to induce and maintain a state of clinically meaningful desensitization to peanut protein, defined as the ability to consume a minimum of 300 mg of

peanut protein with no or mild symptoms. This state of desensitization is hypothesized to be sufficient to protect a peanut-allergic patient in case of an accidental exposure to peanut despite maintaining a peanut-avoidant diet. Although threshold exposure levels for allergic reactions may vary within the peanut-allergic population, a cross-study, retrospective analysis performed by the Voluntary Incidental Trace Allergen Labelling (VITAL) 2.0 study group (Allen, 2014) found that 0.2 mg of peanut protein elicited an allergic reaction in 1% of peanut-allergic patients and 2.1 mg of peanut protein elicited an allergic reaction in 5% of peanut-allergic patients. In 1 well-documented case of accidental peanut ingestion, the amount ingested was calculated to be approximately 45 mg (McKenna, 1997). More recently, an observational survey conducted in France, Belgium, and Luxembourg (MIRABEL study) estimated the amount of food triggering an accidental allergic reaction in 238 peanut-allergic patients. The median estimated real-life eliciting dose was 125 mg (range, 34-177 mg) of peanut protein. The eliciting dose was < 5 mg of peanut protein in 0.9% of patients, 5 to < 50 mg in 34.1%, 50 to < 100 mg in 8.3%, and ≥ 100 mg in 56.7% (Deschildre, 2016). Accordingly, desensitization to at least 300 mg of peanut protein is expected to provide a clinically meaningful level of protection against most accidental exposures to peanut.

1.2 Summary of Relevant Clinical Experience With AR101

AR101 has been evaluated as a treatment for peanut allergy in more than 1000 children and adults in 2 phase 2 studies (ARC001 and ARC002) and 6 phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011); most studies are ongoing.

1.2.1 Phase 2 Studies ARC001 and ARC002

ARC001 was a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic subjects aged 4 to 26 years. The intent-to-treat (ITT) population included 55 subjects: 29 in the AR101 group and 26 in the placebo group. The 2 groups were well matched overall for baseline characteristics, including baseline sensitivity in the screening double-blind, placebo-controlled food challenge (DBPCFC). Subjects began treatment with an initial dose-escalation phase on day 1 at 0.5 mg, dose-escalating up to 6 mg. Subjects tolerating at least 3 mg on day 1 began up-dosing on day 2 at their maximum tolerated dose (3 or 6 mg). Initial dose escalation was discontinued in subjects who could not tolerate at least 3 mg of the study product. Subjects then received AR101 or placebo daily for about 24 weeks, dose-escalating every 2 weeks to the target maintenance dose of 300 mg/day. Twenty-three of 29 AR101-treated subjects (79%) reached the target maintenance dose of 300 mg/day by the end of the up-dosing period and 6 subjects withdrew from the study before reaching the target dose. After a 2-week maintenance period at 300 mg/day, subjects had an exit DBPCFC with up to 600 mg (1043 mg cumulative) of peanut protein or placebo (oat flour). All 23 AR101-treated subjects tolerated at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms during the exit DBPCFC, compared with 5 of 26 subjects in the placebo group, resulting in a treatment difference of 60% ($p < 0.0001$ by Fisher exact test). Further, 18 AR101-treated subjects (62%) tolerated 600 mg (1043 mg cumulative) of peanut protein during the exit DBPCFC,

compared with none in the placebo group, resulting in a treatment difference of 62% ($p < 0.0001$ by Fisher exact test) (Bird, 2018; AR101 investigator brochure).

The open-label follow-on study ARC002 evaluated the safety and efficacy of AR101 in 47 eligible peanut-allergic subjects who participated in the ARC001 originating study. Former placebo-treated subjects began AR101 up-dosing to 300 mg/day, followed by 2 weeks of daily dosing at 300 mg/day and a post-up-dosing DBPCFC. At the post-up-dosing DBPCFC, former placebo-treated subjects exhibited a high rate of desensitization, with 20 of 21 subjects (95%) tolerating the 300 mg (443 mg cumulative) dose of peanut protein. No moderate or severe adverse events were reported and no subject required epinephrine. These findings are consistent with those of the originating study exit DBPCFC in AR101-treated subjects. A total of 40 subjects overall, in both the former placebo-treated and AR101-treated groups, began a 12-week maintenance period at 300 mg/day, followed by a DBPCFC. The DBPCFC was considered passed if the subject tolerated at least 300 mg of peanut protein with no or mild symptoms. Of the 40 subjects overall, 100%, 90%, and 60% of the subjects tolerated a peanut protein dose of 300 mg (443 mg cumulative), 600 mg (1043 mg cumulative), and 1000 mg (2043 mg cumulative), respectively. Moderate or severe adverse events were reported in a minority of subjects at the 2 highest doses. Two subjects each required a single dose of epinephrine (Bird, 2016; AR101 investigator brochure).

The results from these phase 2 AR101 studies demonstrate the persistence of desensitization during maintenance treatment with AR101 at 300 mg/day and indicate that treatment with AR101 may result in a substantially higher tolerated dose of peanut allergen than the dose used for maintenance. Further, desensitization to 300 to 600 mg of peanut protein, the equivalent of approximately 1 to 2 whole peanut kernels (Baumert, 2017), is clinically relevant and expected to reduce the risk of allergic reaction to most accidental exposures to peanut.

1.2.2 Phase 3 Pivotal Study ARC003

ARC003 was an international, randomized, double-blind, placebo-controlled phase 3 study of the efficacy and safety of AR101 in a CODIT regimen in peanut-allergic children and adults aged 4 to 55 years. Preliminary analysis of the final study data is in progress for the database locked in January 2018. Of total of 554 subjects enrolled, 499 subjects were aged 4 to 17 years. The ITT population for the primary analysis included 496 subjects aged 4 to 17 years (372 in the AR101 group and 124 in the placebo group); 67.2% of AR101-treated subjects tolerated a single highest dose of at least 600 mg of peanut protein (1043 mg cumulative) with no more than mild symptoms in the exit DBPCFC compared with 4.0% of placebo-treated subjects, resulting in a treatment difference of 63.2% ($p < 0.0001$; 95% CI: 53.0, 73.3). In addition, 50.3% of AR101-treated subjects tolerated a single highest dose of 1000 mg of peanut protein (2043 mg cumulative), compared with 2.4% of placebo-treated subjects ($p < 0.0001$; 95% CI: 38.0, 57.7). Of subjects aged 4 to 17 years, 296 AR101-treated subjects and 116 placebo-treated subjects had an evaluable exit DBPCFC (completer population). A single highest dose of peanut protein was tolerated with no more than mild symptoms in the exit DBPCFC by 96.3% of AR101-treated completers versus 8.6% of placebo completers for at least 300 mg (443 mg cumulative), 84.5% versus 4.3% for

at least 600 mg (1043 mg cumulative), and 63.2% versus 2.6% for 1000 mg (2043 mg cumulative). The overall safety profile of AR101 was similar to that observed in the phase 2 studies of AR101 and previous studies of peanut OIT (Anagnostou, 2014; Yu, 2012; Varshney, 2011; Blumchen, 2010; Hofmann, 2009; Jones, 2009).

1.3 Summary of Relevant Nonclinical Experience With AR101

AR101 has not been tested in animals. Because AR101 is based on a food that has not shown toxicologic issues, nonclinical studies were not required by regulatory authorities before using AR101 in human studies.

1.4 AR101 Benefits and Risks Assessment

Peanut is a common food with a well understood safety profile, and does not cause apparent side effects in humans except for allergic reactions in patients with peanut allergy.

Based on all available data for AR101 for peanut allergy to date, the benefit-risk profile of the product in this indication is positive. Final data analysis is in progress for the phase 3 study ARC003, and preliminary results indicate robust efficacy and a similar safety profile compared with results in the phase 2 studies.

The AR101 development program has focused on sensitive peanut-allergic individuals, with no subject in study ARC001 able to consume more than 43 mg of cumulative peanut protein during the screening DBPCFC without having an allergic reaction. A total of 79% of the AR101-treated subjects in the ITT population in ARC001 successfully consumed 443 mg of cumulative peanut protein in the exit food challenge, an amount well above the average eliciting dose in an accidental exposure to peanut (Section 1.1), and 100% of AR101-treated subjects in the completer population successfully consumed that amount of peanut protein. Comparable results were seen in the follow-on study ARC002 for subjects receiving AR101 after placebo treatment in ARC001.

While most subjects exposed to food allergen OIT experience adverse events, the majority of adverse events associated with AR101 have been mild to moderate hypersensitivity events, consistent with the low-grade and repeated stimulation of the immune system required to produce desensitization during allergen immunotherapy. A total of 76 subjects from ARC001 and ARC002 (55 unique ARC001 subjects and 21 AR101 rollovers) experienced adverse reactions (treatment-related adverse events). The most common in > 20% of subjects were hypersensitivity (48.7%), abdominal pain (26.3%), and vomiting (21.1%). Other hypersensitivity-related adverse reactions to AR101 have been characterized most frequently (6.6-17.1%) by the following symptoms in decreasing order: urticaria, sneezing, throat irritation, upper abdominal pain, oral pruritus, allergic cough, nausea, nasal congestion, and oropharyngeal pain. All adverse reactions were mild (grade 1) or moderate (grade 2) intensity; none were considered by investigators to be severe. All adverse reactions were nonserious except 1 serious adverse event of hypersensitivity. Consistent with desensitization, the rate of adverse events appears to improve by study phase. Ongoing maintenance treatment with AR101 in study ARC002 has demonstrated continued improved tolerance compared with up-dosing treatment.

Overall, AR101 produced a high rate of desensitization to a clinically meaningful level of peanut protein in phase 2 and 3 studies, indicating that AR101 has the potential to provide treated individuals the benefit of reducing the risk of severe and life-threatening or fatal allergic reactions, which continues to justify the acceptable associated risk.

The AR101 investigator brochure has additional information regarding the safety profile, benefits, and risks of AR101.

1.5 Purpose of the Study

The purpose of this study is to compare the HRQOL of AR101 CODIT in combination with standard of care (peanut avoidance, education) versus standard of care alone in peanut-allergic subjects aged 4 to 17 years, inclusive. The HRQOL of parents/caregivers will also be assessed.

1.6 Rationale for Study Design

The aim of this study is to assess the effects of AR101 treatment on HRQOL of subjects and their parents/caregivers.

Although death resulting from peanut allergy may be rare (Turner, 2015), peanut-allergic individuals and their families may experience low HRQOL due to high levels of anxiety and stress due to increased awareness that peanut allergy may be fatal. Peanut-allergic individuals face a burden of strict peanut avoidance during everyday life, including constant fear of accidental exposure and the inability to predict the severity of allergic reactions due to accidental exposure, despite maintaining a peanut-avoidant diet. Food-allergic individuals frequently have trouble managing their social life because of the need for strict avoidance of the allergenic food, and face the disbelief of others about their condition, often resulting in anxiety, social isolation, and even mental health problems (Mills, 2007). In many cases, the effects of food allergy on quality of life may be greater for caregivers than for the food-allergic children (Valentine, 2011), and the disruption caused by food allergy may have wider implications for the productivity and livelihood of caregivers as well as repercussions for siblings and other family members (Gupta, 2013; King, 2009). Studies in children comparing the HRQOL burden of peanut allergy with type 1 diabetes or rheumatologic disease showed that the burden was comparable to or worse for peanut-allergic children compared with children with these chronic diseases (Avery, 2003; Primeau, 2000), highlighting the need for safe and effective treatments for peanut allergy.

Peanut OIT studies have reported a significant improvement in quality of life following successful desensitization (DunnGalvin, 2017; Anagnostou, 2014; Factor, 2012). In phase 2 studies, AR101 has been shown to produce a high rate of desensitization to a clinically meaningful level of peanut protein. Therefore, important benefits of treatment with AR101 may include significant improvement in the HRQOL for patients and their parents/caregivers, reduced anxiety from the fear of life-threatening anaphylaxis or death from accidental exposure, and the ability to lead a normal day to day life.

Demonstrating a beneficial effect on quality of life and health utility of treatment with AR101 will be informative to certain treatment decision-makers, including payers. However, assessment of HRQOL can be complex for infrequent episodic conditions such as peanut allergy. Food allergy HRQOL is unusual because it is not characterized by daily or frequent symptoms that would allow patients to perceive changes in their health status; rather, it is characterized by beliefs and expectations about the risk of anaphylaxis occurring due to unpredictable accidental exposures and the expected benefits of interventions that reduce this risk. Experiencing an HRQOL benefit from treatment is entirely dependent on patient (and parent/caregiver) knowledge that they have been receiving an active treatment and have been successfully desensitized to the food allergen in question.

An open-label study of HRQOL of patients on standard of care alone and their parents/caregivers will enable a more real-world comparison of treatments than a blinded study. In a blinded study setting, patients in both treatment groups would be required to follow the same study site visit schedule, which is necessarily frequent during up-dosing with food allergens to safely achieve the desired level of desensitization. As this visit frequency is much higher than real-world standard of care practice, it could significantly affect patient and parent/caregiver responses to questionnaires. In an open-label study, the visit schedule for patients receiving standard of care alone can be less frequent and would more closely align with real-world standard of care practice. Therefore, an open-label study design is preferred when assessing the real-world impact of AR101 treatment versus standard of care on HRQOL.

Additionally, previous studies have shown that the DBPCFC also influences HRQOL, because the information it imparts helps reduce uncertainty about the status of the patient's allergy and may reduce anxiety about their ability to manage an allergic reaction arising from accidental exposure (Franxman, 2015; Soller, 2014). As a DBPCFC is not part of the diagnostic pathway for peanut allergy, the ARC009 eligibility criteria include a range of other relevant clinical and patient factors. However, all subjects will have an open-label food challenge (OLFC) approximately 12 months after randomization to study treatment (AR101 or standard of care alone). Because approximately 20% of children are estimated to outgrow their peanut allergy and periodic re-evaluations are recommended (Sampson, 2014; Skolnick, 2001), the OLFC results will be used to confirm peanut allergy for subjects who complete 18 months of standard of care alone as part of the eligibility to receive AR101 in an open-label follow-on study.

HRQOL outcomes have been assessed in randomized, double-blind, placebo-controlled studies of AR101, including ARC003 (PALISADE), ARC007 (RAMSES), and ARC010 (ARTEMIS), and in their open-label follow-on studies. However, ARC009 is anticipated to yield more meaningful HRQOL results and to better reflect the true-life patient/parent (caregiver) experience of AR101 treatment in combination with standard of care compared with standard of care alone, and thus will provide relevant HRQOL evidence for treatment decision-makers.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess proxy- and self-reported disease-specific HRQOL of peanut-allergic subjects aged 4 to 17 years, inclusive, receiving AR101 in combination with standard of care versus standard of care alone for approximately 18 months

2.2 Secondary Objectives

- Safety and tolerability of AR101

To characterize changes over the course of the study in the following:

- Disease-specific HRQOL of parents/caregivers
- Relationship between clinical efficacy of AR101 (change in level of sensitization to peanut allergen) and HRQOL of subjects and parents/caregivers

2.3 Exploratory Objectives

To assess the following:

- Self-reported assessments of control and confidence; reassurance, worry, and severity of allergic reactions based on food challenge outcomes; and overall HRQOL
- Changes in nondisease-specific measures of HRQOL, anxiety, and depression in subjects and parents/caregivers
- Health state utility estimates for economic analysis
- Changes in peanut skin prick test (SPT) mean wheal diameters associated with AR101 treatment
- Changes in control of pre-existing concomitant atopic disease (asthma, allergic rhinitis, atopic dermatitis)
- Relationship between basophil activation, clinical efficacy of AR101, and changes in HRQOL
- AR101 treatment experience among subjects and parents/caregivers

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This is a phase 3b, randomized, open-label, European study of the HRQOL of AR101 in combination with standard of care (AR101 herein) compared with standard of care alone in approximately 200 peanut-allergic subjects aged 4 to 17 years, inclusive. Standard of care includes avoidance of peanuts/peanut-containing foods, and education on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors). HRQOL of parents/caregivers will also be assessed. The safety and tolerability of AR101 will be evaluated.

Eligible subjects will be randomly assigned 2:1 to AR101 treatment or standard of care alone. Randomization will be stratified by age group (4-12 years and 13-17 years). Subjects in both treatment groups and their parents/caregivers will have disease-specific and nondisease-specific HRQOL assessments at screening and periodically thereafter.

Subjects receiving AR101 treatment will have 3 consecutive AR101 dosing periods before exiting (completing) the study: initial dose escalation, up-dosing, and maintenance. Subjects receiving standard of care alone will have approximately 18 months of observation before exiting (completing) the study. Subjects in both treatment groups will have a graded OLFC up to a maximum single highest dose of 1000 mg of peanut protein (2043 mg cumulative), approximately 12 months after randomization.

AR101 Treatment Group

Initial dose escalation: Subjects randomly assigned to AR101 treatment will begin with a stepwise dose escalation of AR101 (up to 5 single doses of 0.5, 1, 1.5, 3, and 6 mg) administered at 20- to 30-minute intervals as tolerated at the study site.

- Subjects who tolerate at least 3 mg of AR101 on day 1 will return to the study site on day 2 to receive a single confirmatory 3 mg dose under direct observation. Subjects who tolerate the 3 mg confirmatory dose with no or mild symptoms that are not dose-limiting will begin the up-dosing period.
- Subjects who do not tolerate at least 3 mg of AR101 on day 1 or day 2 will stop AR101 treatment and discontinue early from the study.

Up-dosing: The up-dosing period will be approximately 6 months (22-40 weeks). Dose escalation will occur approximately every 2 weeks. Daily AR101 doses during up-dosing will be 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of AR101 at each new dose level will be administered under direct observation at the study site; the remaining doses at each dose level will be administered daily at home as tolerated. Subjects able to tolerate 300 mg for 2 weeks will begin the maintenance period. Subjects unable to tolerate 300 mg/day for 2 weeks within 40 weeks of up-dosing will stop AR101 treatment and discontinue early from the study.

Maintenance: Subjects will continue AR101 daily dosing at 300 mg/day for an additional 12 months (52 weeks) with study site visits every 4 weeks. After at least 6 months (up to 7 months) of maintenance treatment (approximately 12 months after randomization/first dose of AR101), subjects will have a graded OLFC up to a maximum single highest dose of 1000 mg of peanut protein (3, 10, 30, 100, 300, 600, 1000 mg [2043 mg cumulative]).

- Subjects who tolerate 1000 mg of peanut protein (2043 mg cumulative) at the OLFC will continue AR101 daily at 300 mg/day and will have the option to consent for a real-world peanut challenge (RWPC) within 4 weeks (preferably within 1 week) after the OLFC. During the RWPC, subjects will eat a food containing 500 to 600 mg of peanut protein under direct observation at the study site. Subjects who complete

the RWPC (regardless of the outcome) will continue daily maintenance treatment with AR101 at 300 mg/day for a total of 52 weeks of maintenance until study exit.

- Subjects who tolerate at least 300 mg but < 1000 mg of peanut protein (2043 mg cumulative) at the OLFC or tolerate 1000 mg of peanut protein (2043 mg cumulative) but do not consent to the optional RWPC will continue daily maintenance treatment with AR101 at 300 mg/day for a total of 52 weeks of maintenance until study exit.
- Subjects who do not tolerate at least 300 mg of peanut protein at the OLFC will stop AR101 treatment and discontinue early from the study.

Standard of Care Treatment Group

Subjects receiving standard of care alone will have approximately 18 months of observation before study exit, with an OLFC approximately 12 months after randomization. Subjects receiving standard of care alone who complete the OLFC will not have an RWPC.

Both Treatment Groups

Early discontinuation: Subjects with unresolved adverse events at early discontinuation or who had GI adverse events of interest will have safety follow-up (Section 5.5).

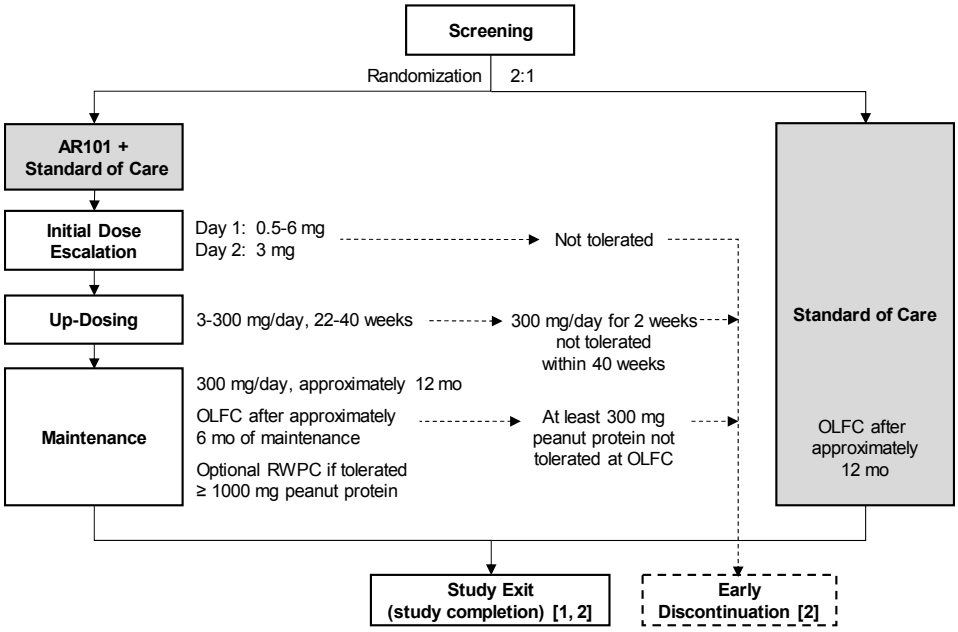
Subjects who discontinue AR101 treatment early before completing 9 months of maintenance, and their parents/caregivers, will complete relevant follow-up HRQOL questionnaires (Section 5.3.1).

Study exit: Subjects with unresolved adverse events at study exit or who had GI adverse events of interest will have safety follow-up (Section 5.5). AR101-treated subjects who complete approximately 12 months of maintenance treatment at 300 mg/day will have the option to enroll in an open-label follow-on study to continue AR101 treatment until it becomes commercially available or its development is terminated. Subjects who receive standard of care alone and complete approximately 18 months of observation will also have the option to receive AR101 treatment in a follow-on study. Subjects may continue to receive AR101 maintenance treatment or standard of care alone in ARC009 if the open-label follow-on study is not activated at their study site when subjects complete their course of treatment/observation.

3.2 Study Schematic

The study schematic is provided in Figure 1.

Figure 1: Study Schematic



AR101 + standard of care: Scheduled visits are day 1, day 2, every 2 weeks during up-dosing (22-40 weeks, approximately 6 months), and every 4 weeks during maintenance (52 weeks, approximately 12 months) until study exit (completion), with an OLFC after approximately 6 months of maintenance and RWPC (if applicable) within 4 weeks (preferably within 1 week) after the OLFC. Questionnaires are completed before randomization and approximately every 3 months thereafter.

Standard of care: Scheduled visits are approximately every 3 months for approximately 18 months until study exit (completion), with an OLFC approximately 12 months after randomization. Questionnaires are completed before randomization and approximately every 3 months thereafter.

[1] Subjects will have the option to receive AR101 in an open-label follow-on study.

[2] Subjects with unresolved adverse events at early discontinuation or study exit or who had GI adverse events of interest will have safety follow-up. Subjects who discontinue AR101 treatment early before completing 9 months of maintenance and their parents/caregivers will complete relevant follow-up HRQOL questionnaires.

GI, gastrointestinal; HRQOL, health-related quality of life; mo, months; OLFC, open-label food challenge; RWPC, real-world peanut challenge.

3.3 Blinding

AR101 treatment will be open label. All subjects, study site personnel (including investigators), and sponsor staff and its representatives will be unblinded to treatment identity.

3.4 Duration of Study

The total duration of treatment (AR101 treatment or standard of care alone) is approximately 18 months for each subject.

The total duration of the study is approximately 30 months (subject to delays during up-dosing or food challenges), assuming an approximate 6-month enrollment period and 24 months between the first subject screened and the last assessment for the last subject.

The end of the study is defined as the last assessment for the last subject in the study.

4 SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of subjects are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1 Inclusion Criteria

Each subject eligible to participate in this study must meet all the following criteria:

1. Aged 4 to 17 years, inclusive, at screening.
2. Written informed consent from subjects, as appropriate per local requirements, and legal guardian/parent (or both parents where required by local authorities) of subjects who are minors.
3. Written assent from subjects who are minors, as appropriate per local requirements.
4. Written informed consent from the parent/caregiver who will complete relevant questionnaires during the study.
5. History of physician-diagnosed immunoglobulin (Ig) E-mediated peanut allergy that includes the onset of characteristic signs and symptoms of allergy within 2 hours of known oral exposure to peanut or peanut-containing food. In general, characteristic signs and symptoms of IgE-mediated allergic reactions are objective and affect the target organs of skin, gastrointestinal (GI) tract, upper/lower respiratory tract, cardiovascular system, or a combination of target organs as follows:

System	**Examples of Symptoms** (Sampson, 2014)
Cutaneous	Pruritus, erythema/flushing, urticaria, angioedema, contact urticaria
Ocular	Pruritus, tearing, conjunctival injection, periorbital edema
Upper respiratory tract	Pruritus, nasal congestion, rhinorrhea, sneezing, hoarseness, laryngeal edema
Lower respiratory tract	Cough, wheezing, dyspnea, chest tightness/pain
Gastrointestinal	Oral pruritus, oral angioedema (lips, tongue, or palate), colicky abdominal pain, nausea, emesis, diarrhea
Cardiovascular	Tachycardia, dizziness, hypotension, loss of consciousness/fainting
Other	Sense of impending doom, uterine cramping/contractions

6. Mean wheal diameter on SPT to peanut ≥ 8 mm greater than the negative saline control at screening.
7. Serum IgE to peanut of ≥ 14 kUA/L at screening.

8. For sexually active females of childbearing potential, use of a highly effective method of birth control, defined as one that results in a low failure rate (ie, < 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.

4.2 Exclusion Criteria

Each subject eligible to participate in this study must **not** meet any of the following exclusion criteria:

1. Uncertain clinical diagnosis of peanut allergy.
2. History of severe or life-threatening anaphylaxis or anaphylactic shock within 60 days before screening.
3. History of eosinophilic esophagitis (EoE); other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"); or recurrent GI symptoms of any etiology.
4. History of a mast cell disorder including systemic mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema.
5. Severe persistent asthma (criteria step 5 or 6; National Heart, Lung, and Blood Institute [NHLBI], 2007) (Table 19).
6. Mild or moderate asthma (criteria steps 1-4; NHLBI, 2007) that is uncontrolled or difficult to control as defined by any of the following:
   - Forced expiratory volume in the first second of expiration (FEV_1) < 80% of predicted, or ratio of FEV_1 to forced vital capacity (FEV_1/FVC) < 75% of predicted, with or without controller medications (aged ≥ 6 years only and able to do spirometry)
   - Inhaled corticosteroid dosing of > 500 µg daily fluticasone (or equivalent based on NHLBI 2007 dosing chart)

- One hospitalization due to asthma within 1 year before screening
- Emergency department visit due to asthma within 6 months before screening

7. History of high-dose corticosteroid medication use (eg, > 3 days at 1-2 mg/kg of prednisone or equivalent) as defined by any of the following:
   - Oral steroid administered daily for > 1 month within 1 year before screening
   - Burst steroid course (oral, intravenous [IV], or intramuscular administration) within 3 months before screening
   - More than 2 burst steroid courses (oral, IV, or intramuscular administration) ≥ 1 week in duration within 1 year before screening
8. History of chronic disease (except asthma, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in a chronic therapeutic regimen, including malignancies within 5 years before screening and autoimmune diseases.
9. History of cardiovascular disease including uncontrolled or inadequately controlled hypertension.
10. Use of beta-blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or tricyclic antidepressants.
11. Unable to discontinue antihistamines 5 half-lives of the medication before the SPT, first day of dose escalation, and food challenges.
12. Lack of an available palatable vehicle food to which the subject is not allergic.
13. Allergy to oat.
14. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector.
15. Use of any therapeutic antibody or any immunomodulatory therapy (including immunosuppressive medications) except aeroallergen or venom immunotherapy used in the maintenance phase within 6 months before screening.
16. Received at least 1 dose of AR101 in another Aimmune-sponsored study.
17. Currently receiving or received within 5 years before screening any type of peanut allergen immunotherapy.
18. Participated in another clinical study within 30 days or 5 half-lives of the investigational product, whichever is longer, before screening.
19. In the build-up phase of immunotherapy for any nonpeanut allergen (ie, has not reached maintenance dosing).
20. Resides at the same place as another subject in any interventional trial sponsored by Aimmune or lives in the same household or is a dependent of a sponsor employee or site staff involved in conducting this study.
21. Pregnant or breastfeeding.
22. Any other condition (concurrent disease, infection, comorbidity, or psychiatric or psychological disorders) or reason that may interfere with the ability to participate in the study, cause undue risk, or complicate the interpretation of data, in the opinion of the investigator or medical monitor.

5 ENROLLMENT AND STUDY PROCEDURES

Enrollment and general study procedures are summarized in the following subsections. The study periods will include screening and treatment. The treatment period for subjects receiving AR101 will include initial dose escalation, up-dosing, and maintenance. The treatment period for subjects receiving standard of care alone will include observation.

The timing of all study procedures is provided in the schedules of activities.

The interactive response system user manual will contain the information needed for registering subject status (eg, assigning subject identification [ID] numbers, indicating screen failure, and end of study).

5.1 Screening Period

The 28-day screening period will be from day -28 through day -1. The screening period will commence after signed informed consent/assent is obtained, followed by assigning a subject ID number and performing screening procedures.

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

5.1.1 Informed Consent

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent and assent (as appropriate) before any study-specific procedures are conducted unless the procedures are part of routine standard of care. The informed consent process must be documented in the subject's source documents (Section 13.1.3).

5.1.2 Subject Identification Numbers

After obtaining signed informed consent/assent, study site personnel will access the interactive response system to assign a subject ID number for each potential study participant. This unique number will be used to identify the subject for the remainder of the study.

For subjects who provide written informed consent/assent and subsequently do not meet eligibility criteria or withdraw consent, study site personnel will document the screen failure or consent withdrawal in the subject's source documents. The documentation will include demographics and medical history, the reason for screen failure, and procedures performed.

5.1.3 Screening Procedures

Screening procedures are listed in the schedule of activities in Appendix 3. All screening procedures must be completed within 28 days after signed informed consent/assent is obtained.

The investigator or designee will assess the eligibility of each subject. All screening procedure results and relevant medical, allergy, and food allergen exposure history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

Rescreening may be considered in certain circumstances on a case-by-case basis following approval from the medical monitor.

HRQOL questionnaires and bespoke questions are to be completed after determination of eligibility and before randomization as required according to Appendix 4 and Appendix 6, and in the order given in Table 1.

5.2 Treatment Periods

5.2.1 Treatment Period Visit Windows

For subjects receiving AR101 treatment, up-dosing visits have a visit window of ±3 days (ie, 3 days before or after the scheduled visit day) and maintenance visits have a visit window of ±7 days. The initial dose-escalation day 1 visit has no visit window. Day 2 should be the next consecutive day after day 1. If circumstances (eg, an intercurrent illness) create a safety risk, day 2 may be delayed up to 7 days after day 1.

For subjects receiving standard of care alone, all study visits have a visit window of ±7 days, except the day of randomization.

Study treatment will continue daily during visit windows. Study product supplies must be considered when scheduling visits.

5.2.2 Randomization Procedures

After confirmation of eligibility and completion of HRQOL questionnaires and bespoke questions per Appendix 4 and Appendix 6, study site personnel will access the interactive response system to assign subjects to randomized study treatment (AR101 treatment or standard of care alone), which is to begin within 28 days after signed consent/assent and should be the same day as randomization. Randomized study treatment may start within 3 days after randomization only if starting the same day is not feasible (eg, for certain unexpected circumstances that may create a safety risk, such as intercurrent illness). A longer window may be allowed on a case-by-case basis following approval from the medical monitor.

5.2.3 General Study Visit Procedures

Day 1 will be the first day of randomized study treatment (AR101 or standard of care alone). All subjects will receive standard of care (Section 5.2.5).

Study procedures will be performed at each visit according to the schedules of activities.

Questionnaires are to be completed in the order given in Table 1. Not all questionnaires are completed at the same visits; questionnaires are to be completed at the study visits indicated in Appendix 4, Appendix 5, and Appendix 6.

The same parent/caregiver should complete all relevant questionnaires during the study. For age-relevant questionnaires, a subject who transitions from one age group to the next age group during the study will complete the version first used. All subject and parent/caregiver questionnaires will be administered before any clinical or physical assessments or dose of AR101, except as follows:

- Bespoke questions on assessment of food challenge outcomes will be administered after the food challenge is completed and the results are explained.
- The European Quality of Life 5-Dimensions health questionnaire (EQ-5D) will also be administered when a severe allergic reaction due to study product or food allergen exposure occurs during an up-dosing visit or at home and 1 week later.

Table 1: Order of Subject and Parent/Caregiver Questionnaires To Be Completed

	Parent/Caregiver	Subject Aged 8 to 12 Years	Subject Aged 13 to 17 Years
1	EQ-5D-5L	EQ-5D-Y	EQ-5D-5L
2	FAQL-PB	FAQLQ-CF, FAIM-CF	FAQLQ-TF, FAIM-TF
3	HADS	Bespoke questions on global assessment of HRQOL (child form)	Bespoke questions on global assessment of HRQOL (teenager form)
4	EQ-5D-Y proxy (for subject aged 4-7 years)		Bespoke questions on control of peanut allergy and confidence in managing allergic reactions (teenager form)
5	FAQLQ-PF, FAIM-PF (for subject aged ≤ 12 years); FAQLQ-PFT, FAIM-PFT (for subject aged 13-17 years)		Bespoke questions on assessment of food challenge outcomes (patient form) [1]
6	Bespoke questions on global assessment of HRQOL (parent/caregiver form)		TSQM-9 (for AR101-treated subject at early discontinuation/study exit)
7	Bespoke questions on control of peanut allergy and confidence in managing allergic reactions (parent/caregiver form)		Bespoke exit questionnaire (patient form, for AR101-treated subject at early discontinuation/study exit)
8	Bespoke questions on assessment of food challenge outcomes (parent/caregiver form) [1]		Qualitative exit interview (for AR101-treated subject at early discontinuation/study exit) [2]
9	TSQM-9 (for AR101-treated subject aged 4-12 years at early discontinuation/study exit)		
10	Bespoke exit questionnaire (parent/caregiver form, for		

	Parent/Caregiver	Subject Aged 8 to 12 Years	Subject Aged 13 to 17 Years
	AR101-treated subject at early discontinuation/study exit)		
11	Qualitative exit interview (for AR101-treated subject at early discontinuation/study exit) [2]		

Questionnaires are to be completed at the study visits indicated in Appendix 4, Appendix 5, and Appendix 6.

[1] To be completed after the end of the observation period for the food challenge (OLFC or optional RWPC) and after the results are explained.

[2] To be conducted in a random sample of parents/caregivers and subjects aged ≥ 13 years at study exit or early discontinuation.

EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels health questionnaire; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; OLFC, open-label food challenge; RWPC, real-world peanut challenge; TSQM-9, Treatment Satisfaction Questionnaire for Medication.

5.2.4 General Procedures for Subjects Receiving AR101 Treatment

Before administration of the first and any subsequent dose of AR101 at the study site, the subject's health status must be at baseline state, including no presence of active wheezing, flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness. The subject must have fully recovered from any previous illness for at least 3 days, depending on the severity of the illness per investigator assessment.

A study physician must always be readily available during dosing at the study site. At minimum, subjects will be evaluated for signs and symptoms of an allergic reaction at 15 to 30 minutes postdose and every 30 minutes thereafter (with vital signs measurements of blood pressure and heart rate), until at least 90 minutes postdose or the end of the observation period, whichever is last. The postdose observation period may be shortened to 30 minutes during maintenance if no allergy symptoms occurred during the previous 3 maintenance visits.

Allergy symptoms will be assessed as follows:

- Symptoms of allergic reactions will be evaluated per Section 8.5.1.
- The tolerability of study product will be evaluated per Section 8.5.1.2.
- The treatment of allergic reactions and dose adjustment of study product will follow guidelines per Sections 8.5.2 and 8.5.3.

On the day after each study site visit, site staff will contact the subject or parent/caregiver by telephone to perform the following:

- Inquire if any adverse events occurred (including allergy symptoms, GI symptoms, and exposure to food allergen).
- Provide guidance in managing adverse events.
- Inquire about compliance with AR101 dosing.

5.2.4.1 Initial Dose-Escalation Procedures

Initial dose-escalation procedures are listed in the schedule of activities in Appendix 4. Subjects may have clear liquids or flavored gelatin during the dosing procedures.

Day 1

Subjects will be required to discontinue antihistamines 5 half-lives of the medication before the first day of dose escalation.

AR101 will be administered in 5 increasing doses in a stepwise manner in 20- to 30-minute intervals as tolerated. The 5 doses and cumulative dose of peanut protein to be consumed on day 1 are shown in Table 2.

Table 2: AR101 Single Doses and Cumulative Dose on Day 1

Dose Number	AR101 Dose (mg peanut protein)	Cumulative Dose (mg peanut protein)
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12

The time points for AR101 dosing and assessments of vital signs and allergic reaction are provided in Table 3. Subjects who develop moderate or dose-limiting symptoms anytime at ≤ 3 mg doses of AR101, severe symptoms at any dose (including 6 mg), or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.5.3.1) will stop dose escalation and discontinue early from the study (Section 5.3).

Table 3: Initial Dose-Escalation Day 1 Procedures

AR101 Dose (Timing) Time Point	Administer AR101	Blood Pressure	Heart Rate	Temp	Assess Allergic Reaction
Predose		X	X	X	
0.5 mg	X				
15-30 min postdose		X	X		X
1 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
1.5 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
3 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
6 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
Every 30 min until at least 90 min after last dose or end of observation per allergy symptoms [2]		X	X		X

[1] If the previous dose was tolerated (Section 8.5.1.2). If the subject has moderate or dose-limiting symptoms anytime at ≤ 3 mg, severe symptoms at any dose (including 6 mg), or uses rescue medications (except ≤ 2 doses of antihistamines, Section 8.5.3.1), stop dose escalation and discontinue the subject early from the study. If at least 3 mg is tolerated, the subject will return for a confirmatory 3 mg dose on day 2.

[2] The length of observation is based on signs/symptoms of allergic reaction per Section 8.5.1.

Min, minutes; temp, temperature.

Day 2

Subjects who tolerate at least 3 mg of AR101 on day 1 will return to the study site on day 2 to receive a single confirmatory 3 mg dose under direct observation. Day 2 should be the next consecutive day after day 1. If circumstances (eg, an intercurrent illness) create a safety risk, day 2 may be delayed up to 7 days after day 1. Subjects who tolerate the 3 mg confirmatory dose with no or mild symptoms that are not dose-limiting will receive an adequate supply of study product to continue daily dosing at home at 3 mg/day in the up-dosing period (Section 5.2.4.2).

Subjects who are unable to return to the study site ≤ 7 days after day 1 for day 2 procedures or who develop moderate or severe symptoms after receiving the 3 mg dose on day 2, or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.5.3.1), will stop AR101 treatment and discontinue early from the study (Section 5.3).

5.2.4.2 Up-Dosing Procedures

Up-dosing procedures and questionnaires are listed in the schedule of activities in Appendix 4.

Up-dosing visits are every 2 weeks for approximately 6 months (minimum 22 weeks if up-dosing proceeds without holding or reducing a dose level; maximum 40 weeks).

The up-dosing period will begin when subjects begin daily dosing with AR101 at 3 mg/day at home for 2 weeks. Up-dosing must not occur until 3 days after oral corticosteroids are discontinued. Subjects who tolerate 3 mg/day will return to the study site to receive the first 6 mg dose. Subjects who tolerate the 6 mg dose at the study site will receive study product to continue daily dosing at home with 6 mg/day for a total of 2 weeks. AR101 dose escalations will continue in this manner up to 300 mg/day as shown in Table 4. Subjects able to tolerate 300 mg/day for 2 weeks will begin the maintenance period (Section 5.2.4.3).

Subjects will stop AR101 treatment if unable to tolerate 300 mg/day for 2 weeks within 40 weeks, or if the dose level cannot be escalated 3 consecutive times (with at least 2 weeks between each escalation attempt) (Section 5.3).

Additional procedures will be performed at the 80 mg and 300 mg up-dosing visits (Appendix 4).

Table 4: Up-Dosing Dose-Escalation Schedule (3-300 mg)

Dose Number	AR101 Dose (mg peanut protein)	Interval (weeks)	Increase From Previous Repeated Dose
1	3	2	Not applicable
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%

Up-dosing begins with the first 3 mg/day dose of AR101 at home.

5.2.4.3 Maintenance Procedures

The maintenance procedures and questionnaires are listed in the schedule of activities in Appendix 5.

Maintenance visits will occur every 4 weeks for 52 weeks (approximately 12 months).

After at least 6 months and up to 7 months of maintenance treatment with AR101 300 mg/day, subjects will have a graded OLFC (Section 9.2.2). Subjects who tolerate 1000 mg of peanut protein (2043 mg cumulative) at the OLFC will continue AR101 at 300 mg/day and will have the option to consent for an RWPC within 4 weeks (preferably within 1 week) after the OLFC (Section 9.2.3). Subjects who complete the RWPC (regardless of the outcome) will continue daily maintenance treatment with AR101 at 300 mg/day for approximately another 4 to 6 months until study exit (total 52 weeks of maintenance).

Subjects who tolerate at least 300 mg but < 1000 mg peanut protein (2043 mg cumulative) at the OLFC or tolerate 1000 mg of peanut protein (2043 mg cumulative) but do not consent to the optional RWPC will continue daily maintenance treatment with AR101 at 300 mg/day for approximately another 5 to 6 months until study exit (total 52 weeks of maintenance).

Subjects who do not tolerate at least 300 mg of peanut protein at the OLFC will stop AR101 treatment and discontinue early from the study (Section 5.3).

5.2.5 Standard of Care Procedures

Standard of care will be provided for all subjects.

Study procedures and questionnaires for subjects receiving standard of care alone are listed in Appendix 6. Study site visits will be approximately every 3 months for approximately 18 months until study exit. Subjects receiving standard of care alone will have an OLFC (Section 9.2.2) approximately 12 months after randomization.

Standard of care will consist of peanut avoidance, and education on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors). Each study site will document its standard of care procedures in source documents.

Subjects will be instructed to follow a peanut-avoidant diet throughout the study.

Peanut/food allergy education will include a comprehensive anaphylaxis action plan per the standard of care at the study site, with at least the following information:

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

An epinephrine auto-injector device will be provided or prescribed as appropriate to subjects and parents/caregivers who do not have one. The expiration date and record of training on the epinephrine auto-injector device must be documented in the subject's source documents.

5.2.6 Unscheduled Visit Procedures

Unscheduled visit procedures are listed in each schedule of activities. Other study procedures may be performed as clinically appropriate.

Unscheduled visits may be performed anytime to assess or follow up adverse events, or at the request of the subject or investigator. The date and reason for the unscheduled visit must be recorded in the source documentation.

5.3 Early Discontinuation

Subjects receiving AR101 treatment: Early treatment discontinuation is defined as *permanent* cessation of study product administration anytime before completing AR101 maintenance treatment at 300 mg/day for approximately 12 months. Subjects who discontinue early will have early discontinuation procedures approximately 14 days after their last dose of AR101 according to the schedule of activities.

Subjects with unresolved adverse events at early discontinuation will have safety follow-up per Section 5.5.

Temporary treatment interruption (eg, due to an adverse event) will not be considered early discontinuation.

Subjects receiving standard of care alone: Early discontinuation of observation is defined as cessation of study participation anytime before the scheduled exit visit. Subjects who discontinue early will have early discontinuation procedures according to the schedule of activities. Subjects with unresolved adverse events at early discontinuation will have safety follow-up per Section 5.5.

The primary reasons for early discontinuation of AR101 treatment or observation are listed in Table 5.

Table 5: Primary Reasons for Early Discontinuation

Category Reason	Comment
Protocol/Investigator-Initiated	
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated using adequate medical intervention or that in the opinion of the investigator or sponsor may lead to undue risk if AR101 treatment were continued, such as the following: • Life-threatening symptoms (CoFAR grade 4), including anaphylaxis resulting in hypotension, neurologic compromise, or mechanical ventilation secondary to study treatment or food challenge. • Severe dose-related allergic hypersensitivity symptoms (CoFAR grade 3) that require intensive therapy (per investigator assessment, but may include interventions such as IV epinephrine, intubation, or admission to an intensive care unit) or are recurrent. • Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma). • Development of biopsy-documented eosinophilic esophagitis. Any adverse event that meets the early discontinuation criteria for study product tolerability or delays as follows: • Tolerability of study product: – Moderate or dose-limiting symptoms at ≤ 3 mg or severe symptoms at any dose on initial dose-escalation day 1 and 2 – The dose was withheld for > 4 weeks for chronic or recurrent gastrointestinal adverse events at ≤ 20 mg/day – Unable to reach the 300 mg/day dose within 40 weeks of up-dosing – Unable to tolerate at least 300 mg of peanut protein at the OLFC • Use of rescue medications: – Treatment with epinephrine, beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids at any AR101 dose (including 6 mg) on initial dose-escalation days 1 and 2 – Treatment with > 2 doses of epinephrine for dose-related allergy symptoms anytime • Dose adjustment of study product: – Unable to escalate the dose level after 3 consecutive failed attempts with at least 2 weeks between each escalation attempt – Unable to tolerate 3 attempts at dose reduction after the occurrence of mild or moderate allergy symptoms, or unable to tolerate 1 attempt at dose reduction after the occurrence of severe symptoms – Missed ≥ 15 consecutive days of study product dosing due to medically indicated circumstances (eg, as part of the treatment for an intercurrent adverse event); missed doses per dose adjustment guidelines in Section 8.5.3.2 are allowed.
Use of prohibited medication	Prohibited concomitant medications are listed in Section 7.4.
Pregnancy	Pregnancy will be followed to delivery or until termination of the pregnancy (Section 8.5.7.2).
Death	

Category Reason	Comment
Investigator decision	Investigators may elect to discontinue a subject's study treatment if they decide it is in the subject's best interest. Select this category if adverse events/intercurrent illness, use of prohibited concomitant therapy, or noncompliance do not apply and the subject preferred to continue treatment.
Major noncompliance with protocol	The medical monitor or investigator may request early discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance. Noncompliance with study product is defined as missed doses for ≥ 8 consecutive days, or missed doses for ≥ 3 consecutive days on > 3 occasions during up-dosing (Section 8.5.5).
Dropout	
Subject decision	Active discontinuation choice by the subject. Subjects may permanently discontinue study treatment anytime for any reason.
Sponsor-Initiated	
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime for any reason as described in Section 13.6. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.
Loss to Follow-Up	
Loss to follow-up	Cessation of participation without notice or action by subject. Loss to follow-up procedures are described in Section 5.6.

CoFAR, Consortium of Food Allergy Research; IV, intravenous; OLFC, open-label food challenge.

5.3.1 Follow-Up HRQOL Questionnaires for Subjects Receiving AR101 Treatment Who Discontinue Early

Subjects receiving AR101 treatment who discontinue early from the study and their parents/caregivers will complete questionnaires at early discontinuation according to Appendix 4 and Appendix 5. In addition, the subject and parent/caregiver will complete the relevant follow-up EQ-5D, Food Allergy Quality of Life Questionnaire (FAQLQ), and Food Allergy Independent Measure (FAIM) questionnaires thereafter according to the timing shown in Table 6 and as indicated in Appendix 4 and Appendix 5.

Table 6: Follow-Up HRQOL Questionnaires for Subjects Receiving AR101 Treatment Who Discontinue Early

Timing of Early Discontinuation	Follow-Up EQ-5D, FAQLQ, and FAIM Questionnaires
Before the start of maintenance	Complete at 12 months and 18 months after day 1
After less than 9 months of maintenance (ie, between maintenance visit week 1 and 41)	Complete at 18 months after day 1

EQ-5D, European Quality of Life 5-Dimensions health questionnaire; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire.

5.4 Study Exit

Study exit procedures are listed in the schedules of activities.

Completion of study exit procedures will be considered as completing the study.

Subjects with unresolved adverse events at study exit or who had GI adverse events of interest will have safety follow-up per Section 5.5.

After the study exit procedures are completed, AR101-treated subjects will have the option to enroll in an open-label follow-on study to continue AR101 treatment until it becomes commercially available or development is terminated. Subjects who received standard of care alone will also have the option to receive AR101 treatment in a follow-on study. Subjects may continue to receive AR101 maintenance treatment or standard of care alone in ARC009 if the open-label follow-on study is not activated at their study site when subjects complete their course of treatment/observation.

5.5 Safety Follow-Up

Safety follow-up procedures are listed in Appendix 7.

Safety follow-up is for subjects with unresolved adverse events at early discontinuation or study exit, or who had GI adverse events of interest. Safety follow-up will continue until the ongoing adverse events resolve or stabilize (after at least 30 days of follow-up after the early discontinuation or exit visit), the subject withdraws consent for follow-up, or the study is terminated. Safety follow-up will continue for 6 months after early discontinuation or study exit for subjects with GI adverse events of interest as described in Section 5.5.1.

For subjects who refuse to come to the study site or if safety follow-up cannot be obtained from alternate contacts, telephone contact must be attempted and documented to review for adverse events. The procedures for loss to follow-up will be followed for subjects who do not respond to telephone calls (Section 5.6).

5.5.1 Safety Follow-Up for Subjects With GI Adverse Events of Interest

For subjects who had GI adverse events of interest (ie, with prolonged dose interruption or that result in or are ongoing at early discontinuation; Section 8.5.6.2), parents/caregivers and subjects aged ≥ 8 years will complete the Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0) questionnaire while the subject is symptomatic, at early discontinuation or study exit, and monthly for 6 months.

In addition, subjects who discontinue early due to GI adverse events will return to the study site monthly for at least 6 months; telephone follow-up by medically qualified personnel may be appropriate in the absence of symptoms, at the discretion of the investigator.

A gastroenterologist referral should be initiated for subjects with GI adverse events persisting > 6 weeks after early treatment discontinuation, and for subjects unable to discontinue using therapies initiated for GI symptoms (eg, H1 or H2 histamine blockers, proton pump inhibitors) by 12 weeks after early treatment discontinuation. Gastroenterologist visits, test results, and endoscopy and endoscopic biopsy results (if applicable) will be documented in the subject's source documents.

Follow-up will continue for chronic or recurrent GI symptoms persisting after 6 months until symptoms resolve or stabilize.

5.6 Loss to Follow-Up

Every reasonable effort must be made to contact any subject apparently lost to follow-up during the study to complete study-related assessments and record outstanding data. After unsuccessful telephone contact, the following is to occur:

- Attempt to contact the subject by mail using a method that provides proof of receipt.
- Try alternate contacts if permitted (eg, primary care providers, referring physician, relatives).
- Document the efforts in the subject's source documents.

If all efforts fail to establish contact, the subject will be considered lost to follow-up.

6 INVESTIGATIONAL PRODUCT INFORMATION

6.1 General Information

The study treatments include AR101 and standard of care. Standard of care includes avoidance of peanuts/peanut-containing foods, and education on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors).

The sponsor will provide AR101 capsules and sachets.

6.2 AR101 Product Characteristics

The AR101 active pharmaceutical ingredient is initially sourced as raw peanuts, Arachis hypogaea, and is processed into food-grade, 12% defatted, roasted peanut flour that contains approximately 50% peanut protein (wt/wt). The peanut flour, which contains peanut allergens, is characterized for its relative composition of key allergenic proteins (Porterfield, 2009) by reversed-phase high performance liquid chromatography (HPLC) and is tested for potency (relative to a reference standard) using an enzyme-linked immunosorbent assay (ELISA) to demonstrate consistency between lots. The AR101 drug product consists of the peanut flour formulated with bulking and flow agents in graduated doses. The drug product is encapsulated in hydroxypropyl methyl cellulose (HPMC) or filled in foil-laminate sachets and supplied in color-coded pull-apart capsules at 5 dosage strengths (0.5, 1, 10, 20, and 100 mg) and 300 mg sachets.

Additional details will be provided in the AR101 investigator brochure and pharmacy manual.

6.2.1 Packaging of AR101

Capsules containing study product are packaged in blister cards that are assembled into dosing kits. Each individual blister of a blister card contains a dose for a single day. Each dosing kit supplies 2 weeks of daily dosing for a single dose level plus another 7 days of daily dosing at the same dose level to accommodate potential visit scheduling issues and wasted or lost product.

Foil-laminate sachets for maintenance dosing are packaged in paperboard cartons for storage and dispensing to study subjects.

The label will vary depending on individual country requirements.

6.2.2 Storage of AR101

The study product should be stored in accordance with the product label and in a secure location at 2°C to 8°C. Temperature excursions may be allowed with specific instructions from Aimmune. Study sites will maintain temperature logs for all refrigerators used to store study product during the study.

6.2.3 Directions for Administration of AR101

The first dose at each dose level will be removed from the dosing kit for the assigned dose level and administered under medical supervision at the study site. Once a dose is removed from the dosing kit, the kit must be dispensed to the subject, held at the study site for destruction, or returned to the sponsor designee according to the procedures in the pharmacy manual. Once opened, dosing kits cannot be used for any other dosing interval or any other subject. Subjects will be instructed to store the dosing kit in the refrigerator and return unused study product to the study site at the next visit.

Dosing Precautions

- The subject must have other food (besides the matrix vehicle used to prepare the dose) in the stomach before taking the dose. The daily dose at home should be taken as part of a meal or heavy snack except on days the dose is given at the study site (the subject should not have an empty stomach).
- Subjects are to avoid activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths) within 3 hours after dosing.
- For subjects engaging in strenuous exercise before the planned dosing time, dosing should be delayed until any signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.
- Dosing should not occur within 2 hours before bedtime.
- In case of illness or symptoms such as wheezing, worsening asthma, fever, vomiting, or diarrhea, the subject or parent/caregiver is to withhold the dose of study product and notify the study site of the symptoms and for possible dose adjustments.

Dose Preparation

The same procedures will be followed for preparing and administering study product at the study site or at home. Study site doses may be prepared by site staff, the subject, or the parent/caregiver under direct supervision of study site staff for training purposes. Doses at home will be prepared by the subject or supervising adult using a vehicle food (eg, applesauce, yogurt, pudding, or other age-appropriate semisolid matrix food) to which the subject is not allergic. The vehicle food volume should be appropriate so the entire dose can be consumed in a few spoonfuls/mouthfuls in one sitting. The vehicle food must not be heated above room temperature before adding the study product or consumption.

Capsules constituting the dose should be pulled apart, gently rolled between the finger and thumb over the vehicle food, and then lightly tapped at the end of each half of the capsule to ensure full delivery of the study product. When using a sachet packet, the packet 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 the study product. Subjects should avoid inhaling the study product, which may induce an allergic reaction or worsening of asthma. The study product should be mixed thoroughly with the vehicle food before administration.

Dose Timing

The study product should be consumed as promptly as possible after mixing. If not consumed within 4 hours after mixing into a vehicle, the mixture should be discarded and a new dose prepared. If preparing a new dose is not feasible (eg, due to limited supply), the study product-vehicle food mixture may be stored for up to 24 hours under conditions appropriate for the vehicle food matrix. If consumption is delayed more than 24 hours, the mixture must be discarded and a new dose mixed and consumed.

The dose should be administered at the same time each day (within a 4-hour period), with a target interval of at least 8 hours between doses. Per investigator judgment, a dose at home may be split into 2 portions (may be unequal) and given 8 to 12 hours apart if tolerability is a concern. The daily dose at home should be taken as part of a meal or heavy snack. Dosing at the evening meal is recommended so that children may be observed and supervised by their parents/caregivers for several hours after dosing.

Subjects must take their dose following their assigned dosing schedule, except as needed to treat an adverse event. Dose modifications due to adverse events are described in Section 8.5.3.

Subjects should not make up a missed dose if more than 6 hours has elapsed after the usual time of dosing. Procedures for missed consecutive doses of study product during up-dosing and maintenance are described in Section 8.5.5.

6.3 Treatment Compliance

Accountability for the study product capsules/sachets will be performed to document compliance with the dosing regimens; noncompliance may lead to early discontinuation (Section 5.3). Subjects or parents/caregivers will be asked to bring all study product packaging, along with any unused capsules/sachets, to study visits. Study site personnel must make reasonable efforts to obtain study product packaging and any unused capsules/sachets from subjects who do not routinely return them at study site visits.

7 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications.

7.1 Prior Medications

All prior medications within 90 days before start of study treatment must be recorded on the case report form and in the subject's source documents.

7.2 Concomitant Medications

All concomitant medications, including those for asthma, allergic rhinitis, and atopic dermatitis, must be recorded on the appropriate case report form. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the subject's source documents.

The use of any medication with known or high potential for cardiovascular side effects is discouraged (eg, antipsychotics, antiarrhythmics, antihypertensives, antineoplastics, cyclooxygenase 2 inhibitors [chronic use], nonsteroidal anti-inflammatory drugs [chronic use]) because subjects may be at increased risk of anaphylaxis that may result in decreased blood pressure when severe. Additionally, epinephrine used to treat anaphylaxis may result

in a sudden increase in blood pressure. An assessment of the benefits and risks of using a medication with known cardiovascular side effects at the same time as AR101 should be discussed with a medical monitor before its use.

Antihistamines and other medications that could interfere with the assessment of an allergic reaction must be discontinued for 5 half-lives of the medication before the SPT, first dose of AR101, and food challenges. The prescribing information must be reviewed to determine the half-life of each medication for the subject's relevant age group.

Symptomatic treatment should be used to supplement dose reduction and not as a substitute for it. Medications for the prophylaxis of symptoms of chronic or recurrent adverse events (eg, H1 or H2 histamine blockers, proton pump inhibitors, inhaled beta-adrenergic agonists) should not be started in advance of symptoms; exceptions may be allowed on a case-by-case basis following approval by the medical monitor. The use of such medications should be minimized, and then discontinued at the earliest opportunity as medically appropriate.

Systemic steroid use is limited to ≤ 3 weeks. Up-dosing must not occur until 3 days after oral corticosteroids are discontinued. Topical steroid use is allowed after an SPT.

7.3 Rescue Medications

All rescue medications (ie, any medication used to treat symptoms of an acute allergic reaction) must be recorded on the case report form. The adverse event requiring the use of rescue medications must be recorded on the adverse event case report form and in the subject's source documents.

Medications for the treatment of individual acute allergic reactions (eg, antihistamine, epinephrine, IV fluids, beta-adrenergic agonist [eg, albuterol by inhaler or nebulizer], oxygen, glucocorticosteroids) are to be used as indicated.

An epinephrine auto-injector device will be provided or prescribed as appropriate to subjects and parents/caregivers who do not have one. The expiration date and record of training on the epinephrine auto-injector device must be documented in the subject's source documents.

7.4 Prohibited Medications

Prohibited medications are presented in Table 7.

Table 7: Prohibited Medications

Medication or Treatment	Comment on Use
Angiotensin II receptor blockers	
Angiotensin-converting enzyme inhibitors	
Beta-blockers (oral)	
Calcium channel blockers	
Immunomodulatory medications, including immunosuppressive medications	Examples include cyclosporine, tacrolimus, antitumor necrosis alpha drugs, anti-IgE drugs, anti-IL-5 or IL-5 receptor-targeted drugs. Before administering a potentially immunomodulatory drug during the study, discuss its use with a medical monitor.
Systemic corticosteroids (oral, intramuscular, intravenous)	Used > 3 consecutive weeks during the study. If used, up-dosing is not allowed during the 3 days after cessation of oral corticosteroids.
Therapeutic immunomodulatory antibodies (experimental or commercially available)	May not be used within 6 months before screening or initiated during the study.
Tricyclic antidepressants	

Ig, immunoglobulin; IL, interleukin.

8 SAFETY CONSIDERATIONS

This section defines the procedures for safety monitoring; requirements and guidelines for identifying, grading, and reporting adverse events; and special safety considerations (assessment of allergy symptoms, treatment, dose adjustment, adverse events of interest, and other notable events).

Study assessments of safety include adverse events, physical examinations, vital signs, peak expiratory flow rate (PEFR), and evaluation of asthma.

8.1 Safety Monitoring

The sponsor will periodically monitor safety data during the study in addition to reviewing individual safety case reports, by examining the incidence and severity of adverse events and serious adverse events and other data (eg, aggregate analysis of data from other AR101 studies). Any relevant safety concerns will be communicated to the investigators, ethics committees (ECs; a global term including institutional review boards, independent ethics committees, research ethics committees, and the like), and regulatory authorities, as appropriate.

8.2 Adverse Event Definitions

This section provides definitions for adverse events, adverse reactions, serious adverse events, unexpected adverse events, suspected unexpected serious adverse reactions (SUSARs), and adverse events of interest for all subjects.

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the study treatment.

Examples of adverse events include the following:

- A new event or experience that was not present at screening/baseline
- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition
- An investigational abnormality (eg, PEFR/FEV_1 measurements, laboratory tests, vital signs) **only if the abnormality is considered clinically significant** by the investigator (eg, associated with clinically significant symptoms, requires additional diagnostic testing or intervention, leads to change in study product dosing or discontinuation from the study)

An adverse event **does not** include the following:

- Pre-existing diseases or conditions present or detected before the start of study treatment that do not worsen
- SPT reactions, unless the reaction or a complication from the procedure is considered a serious adverse event
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure)

Adverse reaction: Any adverse event considered to be caused by the study product.

Serious adverse events: Any adverse event that meets any of the criteria in Table 8 as determined by the investigator or sponsor.

Table 8: Criteria for Serious Adverse Events

Subject Outcome	Comments
Death	Death is an outcome, not an adverse event. The primary adverse event resulting in death should be identified.
Life-threatening	At immediate risk of death from the adverse event (eg, from the combination of severe anaphylaxis and a grade 4 allergic reaction per Section 8.4).
Inpatient hospitalization or prolongation of existing hospitalization	Does not include prolonged hospitalization for extended observation (eg, to watch for a delayed or biphasic reaction) or planned hospitalization (eg, for an elective procedure).
Disability or permanent damage	Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
Congenital abnormality or birth defect	
Important medical event	An event that may jeopardize the health of the subject or require medical or surgical intervention to prevent any of the other outcomes. In general, anaphylaxis classified as an important medical event should require an emergency department visit with intensive therapy (determined by the investigator, but may include interventions such as intravenous epinephrine, intubation, or admission to an intensive care unit; 1-2 intramuscular injections of epinephrine are typically not considered intensive therapy). If anaphylaxis of mild or moderate severity and without administration of intensive therapy is reported as an important medical event, a clinical assessment by the investigator and reason for the assessment must be included in the event narrative.

Source: ICH E2A and US Code of Federal Regulations: 21 CFR 312.32 [75 FR 59961].

Unexpected adverse events: Adverse events for which the nature or severity is not consistent with the reference safety information.

Suspected unexpected serious adverse reactions (SUSARs): Adverse events assessed as serious, related to study product, and unexpected, which are subject to expedited reporting to regulatory authorities and study investigators.

Adverse events of interest: Adverse events of interest are any adverse events (serious or nonserious) identified for ongoing monitoring during the study and require rapid communication by the investigator to the sponsor as described in Section 8.5.6.

8.3 Assessment of Causal Relationship

The investigator will assess the relationship of an adverse event to study product as related or not related (ie, if there is a reasonable possibility that the study product caused the event), and document the relationship in the subject's source documents.

8.4 Assessment of Severity (Intensity)

Severity describes the intensity of a specific adverse event (eg, mild, moderate, severe, life-threatening, or death). The particular event may be of relatively minor medical significance (such as severe headache). Severity is not the same as "serious," which is based on subject/event outcome or action criteria.

Investigators will grade the severity of adverse events. The severity of an adverse event is to be recorded on the case report form and in the subject's source documents.

Three different severity grading systems will be used depending on type of adverse event: allergic reactions, anaphylaxis, or all other adverse events. Brief descriptions of the 3 severity grading systems are provided.

Severity of allergic reactions will be graded using the Consortium of Food Allergy Research (CoFAR) grading system (adapted from Burks, 2012), with scores ranging from 1 (transient or mild discomfort) to 5 (death) (Table 9).

Table 9: CoFAR Severity Grading System for Allergic Reactions

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

Source: Adapted from Burks, 2012.
CoFAR, Consortium of Food Allergy Research.

Severity of anaphylaxis will be graded according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines (Table 10; adapted from Muraro, 2007). The clinical assessment of anaphylaxis is described in Section 8.5.1.1.

Table 10: EAACI Severity Grading System for Anaphylaxis

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Skin and subcutaneous tissues only	Features suggesting respiratory, cardiovascular, or gastrointestinal involvement	Hypoxia, hypotension, or neurologic compromise
Generalized erythema, urticaria, periorbital edema or angioedema	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence

Source: Adapted from Muraro, 2007.
EAACI; European Academy of Allergy and Clinical Immunology.

Severity of all other adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). CTCAE terms are grouped by system organ class, graded 1 to 5, and have unique clinical descriptions of severity for each adverse event based on the general guideline presented in Table 11.

Table 11: NCI CTCAE Severity Grading System for Adverse Events

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death related to adverse event

Source: NCI CTCAE.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

8.5 Special Safety Considerations

This section provides guidelines for the assessment of allergic reactions (including assessment of anaphylaxis and tolerability of a dose), treatment of allergic reactions, study product dose adjustments due to allergic reactions or other reasons, missed doses of study product, adverse events of interest, and other notable events (overdose, pregnancy and other reproductive considerations). The assessment and treatment of allergic reactions resulting from accidental and nonaccidental food allergen exposure should follow the same guidelines as allergic reactions resulting from study product.

8.5.1 Assessment of Allergic Reactions

Allergy symptoms may occur during AR101 treatment as observed in other desensitization protocols. Subjects must be observed for at least 90 minutes after completion of a dose or dose escalation at the study site, with vital sign measurements (blood pressure and heart rate) and assessment for symptoms of allergic reaction performed every 30 minutes. The postdose observation period may be shortened to 30 minutes during maintenance if no allergy symptoms occurred during the previous 3 maintenance visits.

The length of observation will be extended beyond 90 minutes if symptoms of allergic reaction develop as follows:

- Mild symptoms: observe for 90 minutes or at least 1 hour after symptoms resolve, whichever is longer.
- Moderate symptoms: observe for at least 2 hours after symptoms resolve.
- Severe symptoms: observe for at least 3 hours after symptoms resolve either at the study site or an emergency facility, as appropriate. Consider extended overnight observation for subjects experiencing protracted symptoms.

The assessing physician will determine whether the allergy symptoms meet the criteria for dose-limiting symptoms (Section 8.5.1.2).

The severity of symptoms of an allergic reaction will be assessed as described in Section 8.4.

Signs and symptoms of allergic reactions will be recorded on the case report form and in the subject's source documents.

8.5.1.1 Assessment of Anaphylaxis

Anaphylaxis is defined by a number of signs and symptoms, alone or in combination, that occur within minutes up to a few hours after exposure to a provoking agent. Anaphylaxis can be mild, moderate, or severe (Section 8.4). Adverse events of anaphylaxis are considered adverse events of interest and require rapid reporting as described in Section 8.6.2.

Anaphylaxis is likely when any of the following 3 criteria for suspected anaphylaxis is fulfilled (adapted from Sampson, 2006):

1. Acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips/tongue/uvula) and at least 1 of the following:
   - Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEFR, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for the subject (minutes to hours):
   - Involvement of the skin/mucosal tissue (eg, generalized hives, itch/flush, swollen lips/tongue/uvula)
   - Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEFR, hypoxemia)
   - Reduced blood pressure or associated symptoms (eg, hypotonia, syncope, incontinence)
   - Persistent GI symptoms (eg, nausea, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to a known allergen for the subject (minutes to hours) as follows:
   - Infants and children: > 30% decrease from baseline in systolic blood pressure or low systolic blood pressure in children defined as follows:
     – Age 1 to 10 years: < (70 mm Hg + [2 × age])
     – Age 11 to 17 years: < 90 mm Hg

8.5.1.2 Assessment of the Tolerability of a Study Product Dose or Dose Level

The tolerability of a study product dose or dose level will be assessed based on the occurrence of acute allergy symptoms after dosing. When multiple symptoms are present, the severity of the most severe symptom will be used to determine whether symptoms are dose limiting and the dose or dose level is tolerated. Possible assessments of symptom severity, dose-limiting symptoms, and dose tolerability are shown in Table 12.

Table 12: Allergy Symptom Severity and Study Product Dose Tolerability

Symptom Severity	Dose-Limiting Symptom	Assessed Tolerability of Dose
None	No	Tolerated
Mild, oropharyngeal symptoms only	No	Tolerated
Mild, meeting tolerability criteria	No	Tolerated
Mild, not meeting tolerability criteria	Yes	Not tolerated
Moderate, with rare exceptions	Yes	Not tolerated
Severe	Yes	Not tolerated

No Symptoms: A study product dose associated with no allergy symptoms will be assessed as tolerated.

Mild symptoms: For a study product dose associated with mild allergy symptoms, investigator assessment is essential in determining if the symptoms are dose limiting. Based on experience with study product, mild symptoms are not dose limiting if they meet all of the tolerability criteria as follows:

- Are isolated to a single organ system
- Resolve with no medications or with ≤ 2 doses of oral H1 antihistamine
- Do not require administration of epinephrine
- Do not worsen in intensity or distribution over time
- Resolve or show definite signs of resolving in under 1 hour
- Do not include objective wheezing

The study product dose is to be considered not tolerated if mild symptoms do not meet the tolerability criteria as follows:

- Occur in 2 or more organ systems
- Require treatment with 3 doses of oral H1 antihistamine or 1 dose of epinephrine
- Progress in severity or distribution over time
- Continue longer than expected
- Include objective wheezing

If a study product dose associated with mild symptoms that do not meet the tolerability criteria is assessed as tolerated by the investigator, an explanation must be provided on the case report form.

Guidelines for recurrent mild symptoms:

- GI symptoms were the most common subacute, chronic, and recurrent potential symptoms of allergy in phase 2 and 3 clinical studies of AR101.

- Study product may worsen pre-existing atopic dermatitis, seasonal allergies, or asthma, or these symptoms may occur as nonacute allergic reactions to study product.
- Recurrent mild symptoms during several days of dosing at home suggest that the study product dose level is likely not tolerated, even if the symptoms meet the tolerability criteria. For mild dose-related symptoms occurring ≥ 7 times within 2 weeks, the dose level is to be considered not tolerated.

Moderate symptoms: A study product dose associated with moderate allergy symptoms will be assessed as not tolerated, except on rare occasions such as a transient, self-limited symptom in a single organ system that requires no intervention, resolves completely, and is typically subjective.

If a study product dose associated with moderate symptoms is assessed as tolerated by the investigator, an explanation must be provided on the case report form.

Severe symptoms: A study product dose associated with severe allergy symptoms will be assessed as not tolerated.

8.5.2 Treatment of Allergic Reactions

Treatment of allergic reactions is guided by the type of symptoms and severity as determined by the investigator, and supplements dose adjustment. Rescue medications for acute allergic reactions include antihistamines, epinephrine, IV fluids, a beta-agonist (eg, albuterol by inhaler or nebulizer), oxygen, and glucocorticosteroids as indicated (Section 7.3).

Mild acute allergic reactions are mostly transient and self-limiting and require no therapeutic intervention, whereas other reactions may require treatment (generally antihistamines).

Treatment for chronic or recurrent allergic reactions should be used minimally and discontinued as soon as clinically appropriate. Treatment for chronic or recurrent allergic reactions should not be started in advance of symptoms; however, exceptions may be allowed on a case-by-case basis following approval from the medical monitor.

Moderate acute allergic reactions will generally require therapeutic intervention; some rare events may be so transient that no specific treatment is required. For moderate reactions requiring treatment, antihistamines and/or epinephrine is to be administered as indicated.

Severe acute allergic reactions will generally require treatment with epinephrine.

If the severity of the reaction is uncertain, epinephrine administration is likely appropriate.

A medical monitor will be available to answer questions or to assist in decisions related to the study protocol.

8.5.3 Dose Adjustment of Study Product for Allergic Reactions

8.5.3.1 Dose Adjustment of Study Product During Initial Dose Escalation (Days 1 and 2)

Actions that may be taken with study product for allergic reactions occurring on day 1 of initial dose escalation include the following:

- Extend the time interval between study product doses (up to an additional 30 minutes) without any additional treatment.
- Initiate enhanced clinical monitoring (eg, more frequent vital sign monitoring including respiratory rate, auscultation, pulse oximetry).
- Treat with antihistamine and resume study product dose escalation within 60 minutes after the previous dose, if assessed as safe.
- Treat with epinephrine, beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids as necessary. Stop the initial dose escalation and discontinue the subject early from the study if these rescue medications are used at any study product dose (including 6 mg; Section 5.3).
- Stop the initial dose escalation and discontinue the subject early from the study.

The process algorithm for actions to be taken with study product dosing and treatment for acute allergy symptoms on initial dose-escalation day 1 is shown in Figure 2 and described in Table 13. Allergic reactions occurring on day 2 of initial dose escalation will be treated similarly to allergic reactions occurring on day 1.

Figure 2: Management of Study Product Dosing for Allergy Symptoms on Initial Dose-Escalation Day 1

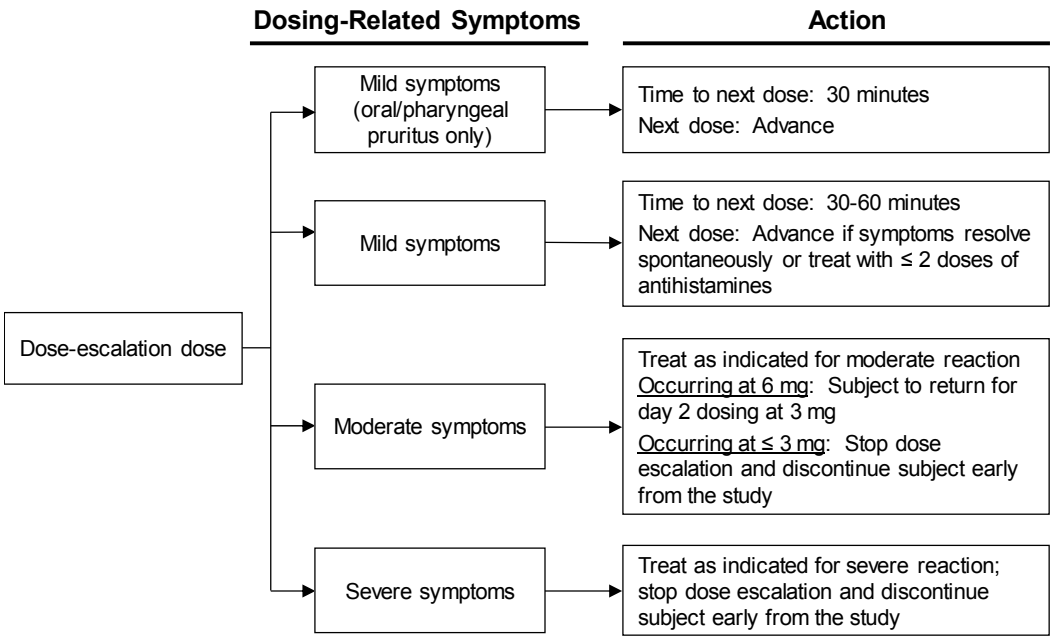


Table 13: Description of Actions to Be Taken With Study Product Dosing for Allergy Symptoms on Initial Dose-Escalation Day 1

Symptoms	Actions
Mild	For oral/pharyngeal pruritus occurring in isolation, advance to the next dose of study product in 30 minutes. For other mild symptoms, either: • Advance to the next dose of study product in 30 to 60 minutes. • Treat with antihistamine, then resume dose escalation within 60 minutes after the previous dose if signs and symptoms resolve to minimal or residual, and the investigator considers continued dosing to be safe. If only 1 or 2 doses of antihistamine are used to treat mild symptoms, the initial dose escalation may continue. If a second medication (eg, epinephrine or a beta-agonist) or > 2 doses of antihistamines are needed, stop the initial dose escalation and discontinue the subject early from the study, even if the symptoms are assessed as mild. Use of epinephrine, although unlikely to be used to treat mild dose-related symptoms, will stop the initial dose escalation and discontinue the subject early from the study.
Moderate	For moderate symptoms not worsening in intensity or distribution over time, the investigator may take a stepwise approach to treatment. If symptoms do not begin to resolve within 30 minutes, initiate therapy with antihistamines or administer epinephrine immediately. Initiate other therapies sequentially or concurrently per investigator judgment. Stop the initial dose escalation and discontinue the subject early from the study if epinephrine, beta-agonist, or > 2 doses of antihistamines are used. For moderate symptoms occurring at challenge doses ≤ 3 mg, stop the initial dose escalation and discontinue the subject early from the study.
Severe	For severe symptoms at any dose, administer the appropriate rescue medications. Stop the initial dose escalation and discontinue the subject from study early.

At any study product dose on initial dose-escalation day 1 or 2 (including 6 mg), treatment with epinephrine, beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids will stop the initial dose escalation and discontinue the subject early from the study (Section 5.3).

8.5.3.2 Dose Adjustment of Study Product During Up-Dosing and Maintenance

Actions that may be taken with study product dosing for allergic reactions during up-dosing and maintenance include the following:

- Administer the next dose of study product at the study site under medical supervision.
- Split the daily dose of study product into 2 portions (may be unequal) given 8 to 12 hours apart.
- Delay the study product dose escalation an additional 1 to 2 weeks.
- Reduce the study product dose level by 1 or 2 dose levels.
- Temporarily withhold study product.
- Stop study product dosing and discontinue the subject early from the study (Section 5.3).

The severity of the symptoms will guide study product dose reductions for both acute and chronic or recurrent symptoms. The process algorithm for dose adjustments for dose-related symptoms occurring at a new dose or dose level given at the study site or for symptoms of a dose-related allergic reaction reported during daily dosing at home is shown in Figure 3 and described in Table 14.

Because of the potential for reduced reliability in reporting symptoms during dosing at home, administration of study product at the study site under medical supervision is strongly encouraged any time that acute allergy symptoms are reported, including mild symptoms occurring with a dose that is suspected to be not tolerated.

The dose escalation may be delayed or the dose level reduced if the tolerability of a dose level is uncertain, at investigator discretion (Section 8.5.1.2).

In general, a reduced dose of study product is to be given at the study site under medical supervision and continued for 2 weeks at home. The lowest dose level of study product is 3 mg.

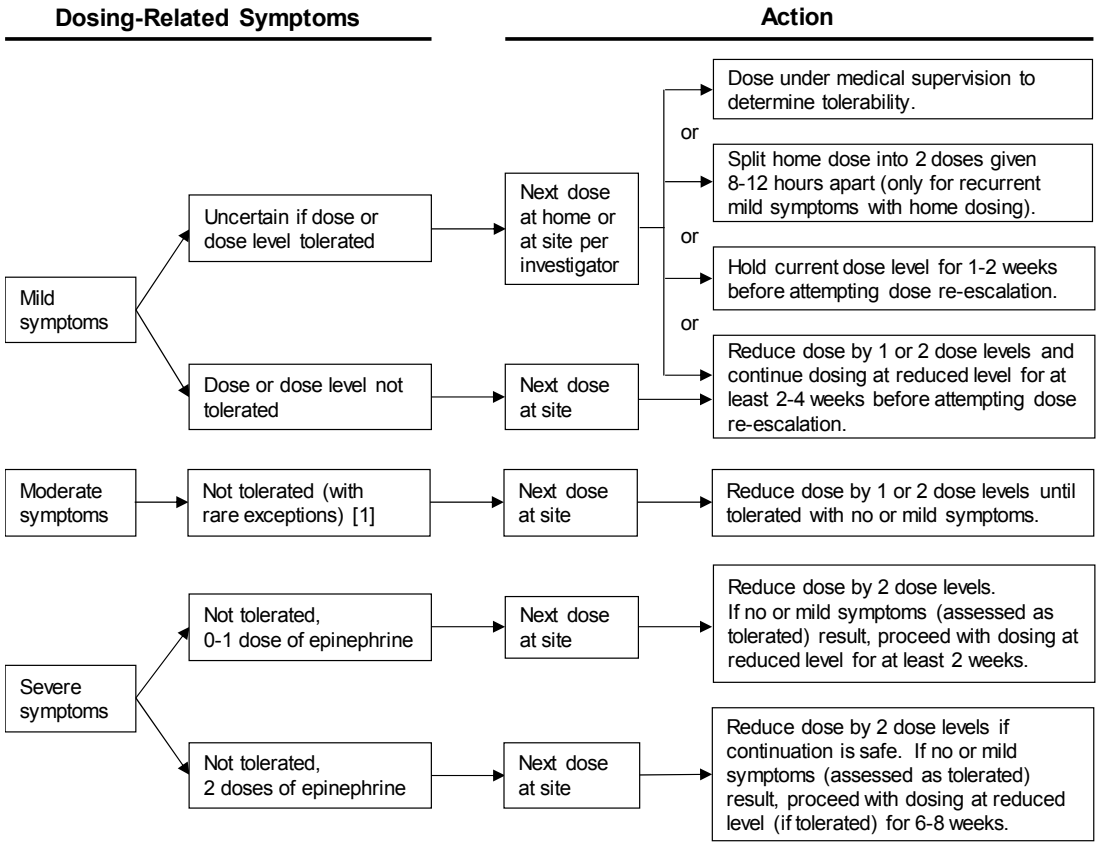
Symptomatic treatment should be used to supplement dose reduction and not as a substitute for it. Symptomatic treatment of adverse events should be discontinued before attempting dose re-escalation at the study site. However, if treatment for chronic or recurrent adverse events cannot be withdrawn successfully, it may be administered concurrently with study product 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 due to administration of epinephrine (Table 15).

Study product dosing will stop and the subject will discontinue early (Section 5.3) if any of the following conditions are met for dose adjustment:

- The dose level cannot be escalated after 3 consecutive failed attempts with at least 2 weeks between each escalation attempt.
- The dose reduction cannot be tolerated after 3 attempts to reduce the dose level.

Figure 3: Management of Study Product Dosing for Allergy Symptoms During Up-Dosing and Maintenance



[1] The actions for moderate symptoms assessed as tolerated are the same as for a dose or dose level associated with mild symptoms assessed as tolerated.

Assess dose tolerability per Section 8.5.1.2.

Table 14: Description of Actions to Be Taken With Study Product Dosing for Allergy Symptoms During Up-Dosing and Maintenance

Symptoms	Actions
Mild	For oral/pharyngeal pruritus occurring in isolation, continue the study product dose level at home for the 2-week dosing interval, unless other symptoms develop. For other mild symptoms and if the study product dose is assessed as tolerated (Section 8.5.1.2), repeat the same dose level the next day, ideally at the study site although it may be given at home. • If no symptoms occur with the repeated dose, continue the dose level for the 2-week dosing interval. • If mild symptoms occur with the repeated dose and the dose is assessed as tolerated, continue the same dose level or reduce the dose to the previous tolerated dose level for the 2-week dosing interval. For other mild symptoms and if the study product dose is assessed as not tolerated (Section 8.5.1.2), give the previous tolerated dose level the next day at the study site. • If the reduced dose is tolerated, continue the dose level for the 2-week dosing interval. • If the reduced dose is assessed as not tolerated, give a second reduced dose (1 or 2 dose levels lower) the next day at the study site. – If the second reduced dose is tolerated, continue this dose level for the 2-week dosing interval. – If the second reduced dose is assessed as not tolerated, discuss early discontinuation with the medical monitor. – If a third reduced dose is considered to be safe after discussion with the medical monitor, give it at the study site under medical supervision. If the dose is assessed as not tolerated, stop study product dosing and discontinue the subject early from the study (Section 5.3). For other mild symptoms and if the study product dose tolerability is uncertain, follow the general guidance in this table for chronic or recurrent mild symptoms.
Mild (chronic or recurrent)	The recurrence of mild dose-related symptoms over several days of dosing at home may suggest that the study product dose level is not tolerated, even if each occurrence could be assessed as tolerated. • For symptoms occurring ≥ 4 times in a week, give the next dose of study product at the study site to assess tolerability. • For symptoms occurring ≥ 7 times during the 2-week dosing interval, the dose level will be considered not tolerated (Section 8.5.1.2). Other actions that may be taken for chronic or recurrent mild symptoms: • Continue daily dosing at home at the current dose level. • Continue the same daily dose for the rest of the 2-week dosing interval, split into 2 portions (may be unequal) and given 8 to 12 hours apart. • Repeat the same dose level at the study site to assess tolerability. • Delay the dose escalation by 1 to 2 weeks. • Give the previous tolerated dose level (1 or 2 dose levels lower based on severity of reaction) at the study site. • Stop study product dosing and discontinue the subject early from the study (Section 5.3). <u>GI symptoms</u> For chronic or recurrent GI symptoms, especially upper GI symptoms, a low threshold for study product dose reduction and for considering early discontinuation is recommended due to the potential for eosinophilic esophagitis. For dose-limiting chronic or recurrent GI

Symptoms	Actions
	symptoms at doses ≤ 20 mg/day, withhold study product for 4 weeks and resume at 3 mg/day with the first dose given at the study site. If 3 mg/day is tolerated, continue this dose level for at least 4 weeks before attempting re-escalation. For dose-limiting chronic or recurrent GI symptoms at doses > 20 mg/day, follow the general guidance in this table based on symptom severity.
Moderate	Administer the previous tolerated dose of study product the next day at the study site. • If no symptoms occur with the reduced dose, continue that dose level for 2 weeks before attempting re-escalation. • If mild symptoms occur at the reduced dose, follow the guidelines for mild symptoms. • If moderate symptoms occur at the reduced dose, give a second reduced dose (1 or 2 dose levels lower) the next day at the study site. – If the second reduced dose is tolerated, continue that dose level for at least 2 weeks before attempting re-escalation. – If mild symptoms occur with the second reduced dose that is assessed as not tolerated, follow the guidelines for mild symptoms. – If moderate symptoms recur at the second reduced dose, discuss early discontinuation with the medical monitor. ▪ If a third reduced dose is considered to be safe after discussion with the medical monitor, give it at the study site under medical supervision. If the dose is assessed as not tolerated, stop study product dosing and discontinue the subject early from the study (Section 5.3). In the rare case that a dose with moderate symptoms is assessed as tolerated, follow the guidelines for mild symptoms and provide a brief explanation for the assessment on the case report form.
Severe	Discuss early discontinuation with the medical monitor. If continuation of study product is considered to be safe, administer a reduced dose at 2 dose levels the next day at the study site under medical supervision. If the reduced dose is tolerated, continue that dose level for at least 2 weeks before attempting re-escalation. If the reduced dose is assessed as not tolerated, stop study product dosing and discontinue the subject early from the study (Section 5.3).

Assess dose tolerability per Section 8.5.1.2.

GI, gastrointestinal.

Appropriate intervention for allergy symptoms associated with a new dose or dose level at the study site or dosing at home will depend on the type and severity of symptoms. The process algorithm for dose adjustments after administration of antihistamines and epinephrine for dose-related allergy symptoms at the study site or at home during up-dosing and maintenance is described in Table 15.

Table 15: Dose Adjustment of Study Product After Treatment With Antihistamines and Epinephrine for Dose-Related Allergy Symptoms During Up-Dosing and Maintenance

Medications	Action
Antihistamines	Continue study product up-dosing if symptoms only require antihistamines. 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	If an administration of epinephrine is required during dose escalation at the study site, reduce the next dose of study product by 2 dose levels and give it at the study site under medical supervision. After 2 weeks at the reduced dose, dose re-escalation at 1 dose level may be attempted at the study site. If epinephrine is required a second time, reduce the next dose of study product by 2 dose levels and give it at the study site under medical supervision. After 6 to 8 weeks at the reduced dose, dose re-escalation at 1 dose level may be attempted at the study site. If epinephrine is required a third time for dose-related allergy symptoms at the study site or at home, stop study product dosing and discontinue the subject early from the study (Section 5.3). If epinephrine is given at home, instruct subjects to go to the nearest emergency department immediately. Reduce the next dose of study product by 1 or 2 dose levels and give it at the study site under medical supervision before resuming dosing at home.

8.5.4 Dose Adjustment of Study Product for Reasons Other Than Allergic Reactions to Study Product

The study product dose level may be continued, reduced, or withheld per investigator judgment in the event of a flare of asthma or atopic disease (eg, atopic dermatitis) not related to study product, or intercurrent illness. In addition, the study product dose level may be temporarily reduced for decreased study product tolerability during menses.

The amount of dose reduction may range from 1 dose level (ie, the previous dose level) to approximately 50% (rounded down to the nearest feasible whole dose) at the discretion of the investigator. The lowest dose level is 3 mg.

If the dose is reduced for reasons other than allergic reactions to study product, the reduced dose will be given for 2 weeks and the subject is to be fully recovered (ie, baseline status) for at least 3 days, depending on the severity of the illness per investigator assessment, before attempting dose re-escalation at the study site. Treatment for an intercurrent illness or disease should be discontinued before dose re-escalation. However, if the treatment cannot be withdrawn successfully, it may be administered concurrently with study product.

The process of dose re-escalation for reduced doses due to reasons other than allergic reactions will depend on the degree and duration of the dose reduction as described in

Table 16. A dose re-escalation attempt should be made within 4 weeks after a dose reduction.

The study product may also be withheld as part of the treatment for intercurrent adverse events at the discretion of the investigator; dose continuation after temporary withholding will follow the procedure for missed study product doses (Section 8.5.5).

Study product dosing will stop and the subject will discontinue early from the study (Section 5.3) if any of the following conditions for dose adjustment are met:

- The dose level cannot be escalated after 3 consecutive failed attempts with at least 2 weeks between each escalation attempt.
- The dose reduction cannot be tolerated after 3 attempts to reduce the dose level.

Table 16: Study Product Dose Re-Escalation After Dose Reduction for Reasons Other Than Allergic Reactions

Dose Reductions	Action
1-4 consecutive days	Resume dosing at the previous dose level under medical supervision at the study site, and continue the 2-week dosing interval.
5-7 consecutive days	Resume dosing under medical supervision at the study site at the reduced dose level or the previous dose level. If re-escalation is tolerated, continue the dose level for at least 2 weeks before attempting re-escalation.
8-14 consecutive days	Resume dosing under medical supervision at the study site at the reduced dose level or 1 dose level above. If re-escalation is tolerated, continue the dose level for at least 2 weeks before attempting re-escalation.

8.5.5 Missed Doses During Up-Dosing and Maintenance

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. Procedures for missed consecutive doses of study product during up-dosing and maintenance are described in Table 17.

Table 17: Procedures for Missed Consecutive Doses of Study Product

Missed Doses	Action
1-2 consecutive doses	Resume next dose at current dose level at home or at the study site.
3-4 consecutive doses	Resume next dose at current dose level under medical supervision at the study site.
≥ 3 consecutive doses on 3 occasions	Stop study product dosing and discontinue the subject early from the study (Section 5.3), unless the dose was withheld for an adverse event or study product dispensing error.
5-7 consecutive doses	Reinitiate next dose at approximately 50% (rounded down to the nearest feasible whole dose) of last tolerated dose under medical supervision at the study site. • If dose is tolerated, resume dose escalation with 1 dose level increase every 1-4 weeks until the dose returns to the last tolerated dose level. • If symptoms occur, follow the dose adjustment guidelines (Section 8.5.3.2).
≥ 8 consecutive doses due to noncompliance	Stop study product dosing and discontinue the subject early from the study (Section 5.3), unless the dose was withheld for an adverse event or study product dispensing error.
8-14 consecutive doses (due to adverse event or study product dispensing error)	Reinitiate next dose at approximately 25% (rounded down to the nearest feasible whole dose) of last tolerated dose under medical supervision at the study site. If the pause in dosing was during maintenance, dosing may be reinitiated at the nearest whole dose that is approximately 50% of the last tolerated dose, at the discretion of the investigator. • If tolerated, resume dose escalation with 1 dose level increase every 1-4 weeks until the dose returns to the last tolerated dose level. • If symptoms occur, follow the dose adjustment guidelines (Section 8.5.3.2).
≥ 15 consecutive days	Stop study product dosing and discontinue the subject early from the study (Section 5.3), unless the dose was withheld for chronic or recurrent gastrointestinal adverse events at ≤ 20 mg/day per Section 8.5.3.2.

8.5.6 Adverse Events of Interest

Adverse events of interest include anaphylaxis, GI adverse events with prolonged dose interruption or that result in or are ongoing at early discontinuation, accidental and nonaccidental food allergen exposure, adverse events with severe symptoms, and use of epinephrine. These events require rapid reporting as described in Section 8.6.2.

8.5.6.1 Anaphylaxis

The assessment of anaphylaxis is described in detail in Section 8.5.1.1. Adverse events of anaphylaxis are considered adverse events of interest and require rapid reporting as described in Section 8.6.2.

8.5.6.2 GI Adverse Events Including Those of Interest

GI symptoms were the most common potential symptoms of allergy to occur on a subacute, chronic, or recurrent basis during phase 2 and phase 3 clinical studies with AR101. For

chronic or recurrent GI symptoms, especially upper GI symptoms, investigators are advised to consider dose reduction of study product or early discontinuation as appropriate due to the potential for EoE. EoE presents with varied symptoms of esophageal dysfunction that differ between children and adults (Dellon, 2013; Dellon, 2011). 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. Investigators are encouraged to request consultation from an outside physician or conduct additional testing to assist in the diagnosis or management of chronic or recurrent GI adverse events at their discretion. If a subject is seen by a gastroenterologist, study site personnel must obtain the records for the visit and the test results, including those from endoscopy and endoscopic biopsy if performed, and retain them in the subject's source documents.

If GI symptoms develop that suggest a chronic or recurrent reaction to study product, the dose level should be reduced (Table 14). The level of the dose reduction should be guided by the severity of the symptoms. Symptomatic treatment is permitted (Section 7.2), but should be used to supplement dose reduction and not as a substitute for it.

GI adverse events of interest are as follows:

- GI adverse events with prolonged dose interruption, defined as withholding study product for > 7 days due to GI adverse events, including dose-limiting chronic or recurrent GI adverse events at doses ≤ 20 mg/day that require the dose to be withheld for 4 weeks
- GI adverse events that result in early discontinuation or are ongoing at early discontinuation

GI adverse events of interest will be considered adverse events of interest and require rapid reporting as described in Section 8.6.2. Parents/caregivers and subjects aged ≥ 8 years will be asked to complete the PEESS v2.0 questionnaire while the subject is symptomatic and thereafter at intervals as described in Section 5.5.1. Additional information about the PEESS v2.0 questionnaire is provided in Section 9.3.4.

After early discontinuation or study exit, subjects who had GI adverse events of interest will have safety follow-up for at least 6 months as described in Section 5.5.1.

8.5.6.3 Accidental and Nonaccidental Food Allergen Exposure

Accidental food allergen exposure is any known or suspected exposure to a food to which the subject is allergic, including peanut, whether or not the exposure results in an adverse event. Nonaccidental food allergen exposure is any intentional exposure to a food to which the subject is allergic, including peanut, whether or not the exposure results in an adverse event.

Accidental and nonaccidental food allergen exposure are considered adverse events of interest and require rapid reporting as described in Section 8.6.2.

Subjects and parents/caregivers will be asked to contact the study site after any food allergen exposure, even if it does not result in symptoms. The subject may be asked to return to the study site.

Subjects and parents/caregivers will complete the EQ-5D questionnaire when allergy symptoms due to food allergen exposure are reported to the study site and assessed as severe, and 1 week later (Appendix 4, Appendix 5, Appendix 6).

8.5.6.4 Adverse Events With Severe Symptoms

Adverse events assessed by investigators as severe by any of the 3 severity grading systems (CoFAR for allergic reactions, Table 9; EAACI for anaphylaxis, Table 10; or CTCAE for all other adverse events, Table 11) are considered adverse events of interest and require rapid reporting as described in Section 8.6.2. Severe allergy symptoms will result in early discontinuation during initial dose-escalation days 1 and 2 (Table 13) and may result in early discontinuation during up-dosing and maintenance (Table 14).

8.5.6.5 Adverse Events Requiring Use of Epinephrine

Adverse events, especially allergic reactions, may result in epinephrine use, as described in Section 8.5.2. Adverse events requiring use of epinephrine are considered adverse events of interest and require rapid reporting as described in Section 8.6.2.

8.5.7 Other Notable Events

Other notable events include overdose and pregnancy.

8.5.7.1 Overdose

An overdose is defined as any dose of study product greater than the prescribed dose within a 24-hour period. The medical monitor must be contacted as soon as possible in the event of a study product overdose. The subject is to be monitored closely for any adverse events and treated for symptoms. The amount of the overdose and its duration are to be recorded in the subject's source documents.

All overdose events require rapid reporting as described in Section 8.6.2 whether or not the event is associated with an adverse event.

8.5.7.2 Pregnancy and Other Reproductive Considerations

Peanut OIT increases the risk of allergic reactions and may increase the risk of anaphylaxis. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus during pregnancy. In

addition, the effect of peanut OIT on the immune system of the mother and fetus during pregnancy is unknown. Therefore, all female subjects of childbearing potential must have a negative serum pregnancy test before the first dose of study product and a negative urine test during the treatment period and must avoid pregnancy during the study.

All postmenarchal female subjects will be provided with age-appropriate counseling and information about contraception per the standard of care at the study site. The information should include adequate information about the use, effectiveness, and side-effects of contraceptive methods, and be conducted in as private a setting as possible using a sensitive, patient-centered approach. Sexually active females 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, < 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.

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

8.6 Adverse Event Reporting

Safety reporting to regulatory authorities will be implemented according to global and country-specific regulations.

To elicit adverse event reports from subjects, the study site personnel should question the subject and parent/caregiver in a general way without suggesting specific symptoms. Adverse events may be identified during study visits.

All signs and symptoms associated with an adverse event, whether or not related to the study product, must be fully and completely documented **for all subjects** (ie, both treatment groups) on the adverse event case report form and in the subject's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form, as well as documented in the subject's source documents.

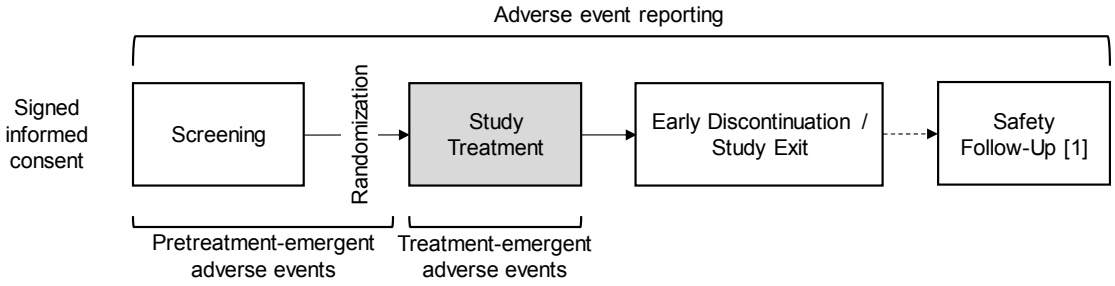
Adverse event terms should include a diagnosis, as available, and is preferred to listing all the individual signs and symptoms. If the diagnosis is not known, the investigator is to record each sign and symptom as an individual adverse event. For multiple symptoms of allergic reactions/hypersensitivity, each individual symptom is to be entered separately on the case report forms.

8.6.1 Adverse Event Reporting Period

Collection and reporting of adverse event information will begin at the time the screening informed consent/assent form is signed and will continue for all subjects through early discontinuation or study exit (Figure 4). Adverse event reporting and follow-up will continue after early discontinuation or study exit in the following circumstances:

- Subjects with ongoing adverse events will have safety follow-up for at least 30 days until the adverse events resolve or stabilize, the subject withdraws consent for follow-up, or the study is terminated.
- Subjects who have GI adverse events of interest (Section 8.5.6.2) will have safety follow-up for 6 months or until chronic or recurrent GI symptoms resolve or stabilize, whichever is last.

Figure 4: Adverse Event Reporting Period



[1] Subjects with unresolved adverse events or gastrointestinal adverse events of interest at early discontinuation or study exit will have safety follow-up.

All adverse events from the start of study treatment must be documented on the adverse event case report form and in the subject's source documents. Any event occurring during screening and before the first dose must also be documented on the appropriate case report form and in the subject's source documents.

8.6.2 Reporting for Serious Adverse Events, Adverse Events of Interest, and Other Notable Events

Serious adverse events, adverse events of interest, and other notable events for **all subjects** (ie, both treatment groups) require rapid reporting **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.

The contact information for submission of information for reportable events is as follows:

Name: ProPharma Group

Email: clinicalsafety@propharmagroup.com

The initial report should include, at minimum, the following:

- Study number (ARC009)
- Site name and number
- Investigator name
- Subject ID number, sex, and age (unless omitted per local regulations)
- Details of study treatment
- The date of the report
- A description of the event (event term, severity)

Initial reporting should not be delayed, and additional follow-up reports may be submitted as new information becomes available. Follow-up reports should include date of onset, study site/hospital records, discharge summary, resolution date, treatment and action for the event, assessment of relatedness to study product, and any other applicable information.

8.6.2.1 Serious Adverse Events Reporting

Study site personnel will report serious adverse events to the sponsor or designee using a serious adverse event report form in accordance with the information requested on the form. Serious adverse events reported to the investigator after the safety reporting period are to be reported to the sponsor if the investigator assesses the event as related to the study product.

If a subject dies, the serious adverse event report should include the cause of death as the event term (with fatal outcome), whether the event leading to death was related to study

product, the autopsy findings if available, and any other supporting data (eg, death certificate, hospital/study site notes).

8.6.2.1.1 Expedited Reporting of Serious Adverse Events by the Sponsor and Periodic Reporting

The sponsor will determine whether a serious adverse event meets the criteria for expedited reporting to regulatory authorities, ECs, and investigators, as applicable in accordance with International Council for Harmonisation (ICH) E2A and ICH E6, and will ensure that reports are provided in compliance with the required timing.

Additionally, the sponsor will submit to regulatory authorities all safety updates and periodic reports as required by applicable national and international requirements including but not limited to ICH E6 and ICH E2F.

8.6.2.2 Adverse Events of Interest Reporting

Nonserious adverse events of interest will require rapid reporting (**within 24 hours**) regardless of severity, causality assessment, and where the event occurred (at the study site or elsewhere). Adverse events of interest include the following, and details for each are provided in the referenced sections:

- Anaphylaxis (Section 8.5.1.1).
- GI adverse events with prolonged dose interruption defined as withholding study product for > 7 days due to GI adverse events, or GI adverse events that result in early discontinuation or are ongoing at early discontinuation (Section 8.5.6.2).
- Accidental/nonaccidental food allergen exposure (Section 8.5.6.3). Rapid reporting is required regardless of whether the exposure resulted in an adverse event.
- Adverse events with severe symptoms (Section 8.5.6.4). Intended for adverse events that do not meet the criteria for other adverse events of interest.
- Use of epinephrine (Section 8.5.6.5). Use of epinephrine for a serious adverse event or other event requiring rapid reporting (eg, anaphylaxis, food allergen exposure) does not need to be reported separately.

Adverse events of interest are to be reported using a nonserious adverse event of interest report form. Adverse events of interest meeting serious adverse event criteria are to be reported as serious adverse events.

8.6.2.3 Other Notable Events Reporting

Reportable events in this category include pregnancy and overdose.

Pregnancy: Although pregnancy is not considered an adverse event, pregnancy must be reported on a pregnancy notification form. The pregnancy will be followed to delivery or

termination, and reporting the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Overdose: Overdose will be reported using an overdose report form.

9 ASSESSMENT OF HRQOL, EFFICACY, AND SAFETY

Descriptions of questionnaires, measures of desensitization to peanut, and other tests for the assessment of study endpoints and other assessments are provided in the following subsections.

9.1 Assessments of HRQOL and Other Subject- and Parent/Caregiver-Reported Outcomes

The primary analyses will use scores from a family of proxy- and self-reported disease-specific HRQOL measures to assess the HRQOL of peanut-allergic subjects treated with AR101 or standard of care alone during the study. The relevant disease-specific HRQOL questionnaires include the FAQLQ-PF (parent form), FAQLQ-PFT (parent form teenager), FAQLQ-CF (child form), FAQLQ-TF (teenager form), FAIM-PF (parent form), FAIM-PFT (parent form teenager), FAIM-CF (child form), and FAIM-TF (teenager form).

Other endpoints on HRQOL and subject- and parent/caregiver-reported outcomes will be assessed using scores from the following:

- Food Allergy Quality of Life - Parental Burden (FAQL-PB)
- Nondisease-specific instruments (Hospital Anxiety and Depression Scale [HADS] and EQ-5D) and relevant subdomains
- Bespoke questions for global assessment of HRQOL
- Bespoke questions to assess control of peanut allergy and confidence in managing allergic reactions
- Bespoke questions to assess experiences related to food challenges
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Bespoke exit questionnaire for parents/caregivers and subjects aged ≥ 13 years

A semistructured qualitative exit interview will be conducted at study exit or early discontinuation in a random sample of parents/caregivers and subjects aged ≥ 13 years.

The instruments to be used for subject- and parent/caregiver-reported HRQOL and other outcomes are summarized in Table 18 and are to be completed in the order given as required.

The same parent/caregiver should complete all relevant questionnaires during the study. For age-relevant questionnaires, subjects who transition from one age group to the next age group during the study will complete the version first used.

Not all questionnaires are completed at the same visits. The schedules for questionnaires are presented in Appendix 4 and Appendix 5 for subjects receiving AR101 and Appendix 6 for subjects receiving standard of care alone.

Table 18: Summary of Instruments for Subject- and Parent/Caregiver-Reported HRQOL and Other Outcomes

Questionnaires/Bespoke Questions	Individual Assessed	Completed by
EQ-5D-5L	Parent/caregiver and subject aged 13-17 years	Parent/caregiver and subject
FAQL-PB	Parent/caregiver	Parent/caregiver
HADS	Parent/caregiver	Parent/caregiver
EQ-5D-Y proxy version	Subject aged 4-7 years	Parent/caregiver
EQ-5D-Y	Subject aged 8-12 years	Subject
FAQLQ-PF and FAIM-PF	Subject aged ≤ 12 years	Parent/caregiver
FAQLQ-PFT and FAIM-PFT	Subject aged 13-17 years	Parent/caregiver
FAQLQ-CF and FAIM-CF	Subject aged 8-12 years	Subject
FAQLQ-TF and FAIM-TF	Subject aged 13-17 years	Subject
Bespoke global assessment of HRQOL		
Parent/caregiver form	Subject	Parent/caregiver
Teenager form	Subject aged ≥ 13 years	Subject
Child form	Subject aged 8-12 years	Subject
Bespoke assessment of control and confidence		
Parent/caregiver form	Parent/caregiver	Parent/caregiver
Teenager form	Subject aged ≥ 13 years	Subject
Bespoke assessment of food challenge outcomes		
Parent/caregiver form	Parent/caregiver	Parent/caregiver
Patient form	Subject aged ≥ 13 years	Subject
TSQM-9	AR101-treated subject	Subject aged ≥ 13 years and parent/caregiver of subject aged 4-12 years
Bespoke exit questionnaire		
Parent/caregiver form	Parent/caregiver of AR101-treated subject	Parent/caregiver
Patient form	AR101-treated subject aged ≥ 13 years	Subject

Questionnaires/Bespoke Questions	Individual Assessed	Completed by
Qualitative exit interview [1]	Parent/caregiver of AR101-treated subject and AR101-treated subject aged ≥ 13 years at study exit or early discontinuation	Parent/caregiver and subject

The same parent/caregiver should complete all relevant questionnaires during the study. For age-relevant questionnaires, a subject who transitions from one age group to the next age group during the study will complete the version first used.

[1] To be conducted in a random sample of parents/caregivers and subjects aged ≥ 13 years at study exit or early discontinuation.

EQ-5D, European Quality of Life 5-Dimensions health questionnaire; EQ-5D-5L, EQ-5D 5-Levels; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; TSQM-9, Treatment Satisfaction Questionnaire for Medication.

9.1.1 FAQLQ-PF, FAQLQ-PFT, and FAIM Questionnaires

The FAQLQ-PF will be completed by parents/caregivers of subjects aged ≤ 12 years and the FAQLQ-PFT will be completed by parents/caregivers of subjects aged 13 to 17 years. The FAQLQ-PF questionnaire includes 3 domains (emotional impact, food anxiety, and social and dietary limitations) and consists of 26 items for children aged 4 to 6 years and 30 items for subjects aged 7 to 12 years (DunnGalvin, 2008). The FAQLQ-PFT includes 4 domains (with social and dietary limitations scored as separate domains) and consists of 27 items. Each item contains response options from 0 (no impact) to 6 (extreme impact) and is scored on a 7-point scale from 1 to 7. For the FAQLQ-PF, each domain is scored as an average of the item scores, with the total score representing the mean of the 3 domain scores. For the FAQLQ-PFT, the total score is the average of completed item scores.

The FAIM questionnaires were developed to measure construct validity of the FAQLQ (van der Velde, 2010). The FAIM-PF and FAIM-PFT measure parent/caregiver perception of disease severity and expectation of allergen exposure outcome for their child/teenager. The FAIM-PF will be completed by parents/caregivers of subjects aged ≤ 12 years and consists of 8 items. The FAIM-PFT will be completed by parents/caregivers of subjects aged 13 to 17 years and consists of 4 items. Each question contains response options from 0 (low likelihood of a bad outcome) to 6 (extremely likely to have a bad outcome) and is scored on a 7-point scale from 1 to 7.

9.1.2 FAQLQ-CF/FAIM-CF and FAQLQ-TF/FAIM-TF Questionnaires

Subjects aged 8 to 12 years will complete the FAQLQ-CF (child form), which includes 4 domains (emotional impact, allergen avoidance, dietary restrictions, and risk of accidental exposure) and consists of 24 items (Flokstra-de Blok, 2009). Subjects aged 13 to 17 years will complete the FAQLQ-TF (teenager form), which includes 3 domains (with dietary

restrictions and allergen avoidance combined into 1 domain) and consists of 23 items (Flokstra-de Blok, 2008). Each item contains response options from 0 (no impact) to 6 (extreme impact) and is scored on a 7-point scale from 1 to 7. Each domain is scored as an average of the items completed, with the total score representing the mean of all items completed.

The FAIM-CF and FAIM-TF consist of 6 items each; each item contains response options from 0 (low likelihood of a bad outcome) to 6 (extremely likely to have a bad outcome) and is scored on a 7-point scale from 1 to 7. Subjects completing the FAQLQ-CF/FAIM-CF or FAQLQ-TF/FAIM-TF are to provide their own responses. The parent/caregiver can help read or explain the meaning of a question, but the response should be selected only by the subject.

9.1.3 FAQL-PB Questionnaire

The FAQL-PB questionnaire is a self-administered, 17-item questionnaire that measures quality of life in parents/caregivers of children with food allergy (Knibb, 2013; Cohen, 2004). Each item is presented on a 7-point Likert scale from 1 (not troubled) to 7 (extremely troubled), and the index is scored as a summated rating scale, with a higher FAQL-PB score indicating a greater burden on the family.

9.1.4 HADS Questionnaire

The HADS consists of 7 questions to assess anxiety and 7 questions to assess depression over the last week (Zigmond, 1983). Each question is presented on a 4-point scale from 0 to 3. Composite scores are categorized as follows: 0 to 7, normal; 8 to 10, mild; 11 to 14, moderate; and 15 to 21, severe.

9.1.5 EQ-5D Questionnaires

EQ-5D questionnaires are used to assess health utility in subjects and parents/caregivers. The EQ-5D-5L (5-Levels) is completed by parents/caregivers and subjects aged 13 to 17 years. The EQ-5D-5L consists of a descriptive system of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and 5 levels (1, no problems; 2, slight problems; 3, moderate problems; 4, severe problems; 5, extreme problems), and a visual analog scale from 0 (worst health) to 100 (best health) (van Reenen, 2015). Subjects aged 8 to 12 years will complete the EQ-5D-Y (Youth) questionnaire, which consists of a descriptive system of 5 dimensions and 3 levels (no problems, some problems, and a lot of problems), and a visual analog scale (van Reenen, 2014). Parents/caregivers of subjects aged 4 to 7 years will complete the EQ-5D-Y proxy version, which rates how the parent/caregiver rates the health of the child.

9.1.6 Assessments of Control and Confidence

The parent/caregiver form and teenager form for the assessment of control of peanut allergy and confidence in managing allergic reactions each include 2 items: 1 related to perceived

control over the subject's peanut allergy and 1 related to perceived confidence in managing allergic reactions to peanut. Each item is scored on a 4-point scale from 1 to 4, with lower values indicating less control or confidence. The parent/caregiver will complete the parent/caregiver form and subjects aged ≥ 13 years will complete the teenager form.

9.1.7 Global Assessments of HRQOL

The parent/caregiver form and teenager form for global assessment of HRQOL each include 5 items: 4 items related to the subject's HRQOL (with the same domains as the related FAQLQ questionnaires) and 1 global HRQOL item. The child form does not include the global HRQOL item. Each item is scored on a 5-point scale from 1 to 5, with lower values indicating better HRQOL. The parent/caregiver will complete the parent/caregiver form, subjects aged ≥ 13 years will complete the teenager form, and subjects aged 8 to 12 years will complete the child form.

9.1.8 Assessments of Food Challenge Outcomes

The parent/caregiver form and patient form for the assessment of food challenge outcomes each include 3 items. The items assess the parent/caregiver and subject's level of reassurance based on the result of the food challenge, level of worry about future allergic reactions due to accidental peanut exposure based on the result of the food challenge, and rating of severity of the allergic reaction to the food challenge. Each item is scored on a 4-point scale from 1 to 4, with lower values indicating no reassurance/worry or no reaction. The parent/caregiver will complete the parent/caregiver form and subjects aged ≥ 13 years will complete the patient form.

9.1.9 TSQM-9 Questionnaire

The generic TSQM-9 questionnaire is a 9-item instrument used to evaluate subject treatment satisfaction (Bharmal, 2009). Higher scores indicate greater treatment satisfaction.

9.1.10 Exit Questionnaire

Bespoke exit questionnaires were developed to assess parent/caregiver and subject experience and satisfaction with study treatment. The exit parent/caregiver form includes items related to both parent/caregiver and subject experience with study treatment, and will be completed by the parent/caregiver. The exit patient form includes items related to subject experience with study treatment, and is completed by subjects aged ≥ 13 years.

9.1.11 Qualitative Exit Interview

The qualitative exit interview will follow a semistructured interview guide and explore subject and/or parent/caregiver experience living with peanut allergy before and after AR101 treatment, as well as their treatment experience. The duration of the exit interview will be up to 60 minutes. The exit interview will be scheduled as soon as possible after the study exit or early discontinuation visit, at a time convenient for the subject and/or parent/caregiver, and

may be conducted by telephone. The exit interview will be conducted in a random sample of parents/caregivers and subjects aged ≥ 13 years at study exit or early discontinuation.

9.2 Measures of Desensitization

Desensitization will be measured using the SPT, OLFC, and RWPC according to the schedules of activities.

9.2.1 Skin Prick Test

Peanut SPT mean wheal diameters will be measured to assess the immunomodulatory effects of AR101 treatment. SPTs for peanut extract will be performed after antihistamines are discontinued for at least 5 half-lives of the medication, according to the schedules of activities. Details are provided in the study manual.

9.2.2 Open-Label Food Challenge

Subjects receiving AR101 treatment will have an OLFC after at least 6 months (up to 7 months) of maintenance treatment with AR101 at 300 mg/day to assess the level of desensitization to peanut protein. Subjects receiving standard of care alone will have an OLFC approximately 12 months after randomization.

The OLFC will be conducted within a single day and consistent with accepted food challenge procedures. The OLFC will conditionally test single doses of peanut protein (3, 10, 30, 100, 300, 600, and 1000 mg) using a food challenge mixture containing defatted peanut flour, administered sequentially at 20- to 30-minute intervals up to a single highest dose of 1000 mg of peanut protein (2043 mg cumulative). The OLFC is described in detail in Appendix 1, including all requirements before, during, and after the OLFC.

9.2.3 Real-World Peanut Challenge

Subjects receiving AR101 treatment who tolerate the 1000 mg (2043 mg cumulative) OLFC dose of peanut protein will have the option to consent for an RWPC under direct observation at the study site within 4 weeks (preferably within 1 week) after the OLFC. The RWPC is described in detail in Appendix 2, including all requirements before, during, and after the RWPC.

9.3 Safety and Other Assessments

9.3.1 Lung Function Tests and Assessments of Asthma Control

Lung function tests will be performed according to the schedules of activities. Lung function tests include PEFR for subjects aged ≥ 6 years and attempts of PEFR for subjects aged 4 to 5 years. Spirometry (FEV_1) will be obtained if PEFR shows a clinically relevant reduction or for symptoms of clinical deterioration (eg, active wheeze on physical examination).

For subjects with asthma, the evaluation of asthma severity will be assessed using the classification in Table 19.

Asthma control in subjects with pre-existing asthma will be assessed using scores from the Asthma Control Test (ACT) (Schatz, 2006) and by the incidence of asthma rescue medication use. The ACT is a self-administered, 5-item questionnaire for subjects aged ≥ 12 years, used to evaluate the level of asthma control in the last 4 weeks. Each question is presented on a 5-point scale, with lower numbers indicating worse asthma control. A composite score of more than 19 indicates well-controlled asthma.

The Childhood Asthma Control Test (C-ACT) is a 7-item questionnaire used to evaluate the level of asthma control in subjects aged 4 to 11 years with pre-existing asthma (Liu, 2007). Subjects complete the first part of the questionnaire, which consists of 4 questions and a choice of 4 responses from 0 (worse asthma) to 3 (controlled asthma) for each question. The parent/caregiver may help the subject read or understand the question if needed, but only the subject should select the response. The parent/caregiver completes the second part of the questionnaire, which consists of 3 questions and a choice of 6 responses from 0 (worse asthma) to 5 (controlled asthma) for each question. Parents/caregivers are asked to recall asthma symptoms in the last 4 weeks and complete their portion of the questionnaire without influence from the subject's responses. A composite score of more than 19 indicates well-controlled asthma.

Table 19: Evaluation of Asthma Based on NHLBI Criteria

Classification	Intermittent (Step 1)	Persistent: Mild (Step 2)	Persistent: Moderate (Step 3 or 4)	Persistent: Severe (Step 5 or 6)
Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Night-time awakenings				
Subject aged 0-4 years	0	1-2 times/month	3-4 times/month	> 1 time/week
Subject aged ≥ 5 years	≤ 2 times/month	3-4 times/month	> 1 time/week but not nightly	Often 7 times/week
Short-acting inhaled beta$_2$-agonist use	≤ 2 days/week	> 2 days/week, but not daily (and not more than once a day for subject ≥ 12 years)	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function				
Subject aged 0-4 years	Not applicable	Not applicable	Not applicable	Not applicable
Subject aged 5-11 years	Normal FEV_1 between exacerbations FEV_1 > 80% predicted FEV_1/FVC > 85%	FEV_1 ≥ 80% predicted FEV_1/FVC > 80% and ≤ 85%	FEV_1 ≥ 60% but < 80% predicted FEV_1/FVC ≥ 75% and ≤ 80%	FEV_1 < 60% predicted FEV_1/FVC < 75%
Subject aged ≥ 12 years	Normal FEV_1 between exacerbations FEV_1 > 80% predicted FEV_1/FVC normal [1]	FEV_1 ≥ 80% predicted FEV_1/FVC normal [1]	FEV_1 ≥ 60% but < 80% predicted FEV_1/FVC reduced ≤ 5% [1]	FEV_1 < 60% predicted FEV_1/FVC reduced > 5% [1]

Adapted from NHLBI, 2007.

[1] Normal FEV_1/FVC by age: 8-19 years, 85%; 20-39 years, 80%; 40-59 years, 75%; 60-80 years, 70%.

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

9.3.2 TNSS Questionnaires

The Total Nasal Symptom Score (TNSS) is used to assess the severity of allergic rhinitis and will be administered only to subjects with pre-existing allergic rhinitis. The TNSS (short form) consists of 3 questions that address nasal obstruction, rhinorrhea, and nasal itch/sneezing (Downie, 2004). 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.

9.3.3 SCORAD Index

The scoring atopic dermatitis (SCORAD) index is used to assess the severity of atopic dermatitis and will be administered only to subjects with pre-existing atopic dermatitis (European Task Force on Atopic Dermatitis, 1993). The SCORAD index is based on the combination of the following:

- Extent of lesions (accounts for about 20% of the total score).
- Intensity, based on 6 items (erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness), each graded from 0 (absent) to 3 (severe) according to reference photographs (accounts for about 60% of the total score).
- Subjective items (pruritus and sleep loss). The subject (aged >7 years) or parent/caregiver will indicate the average value for pruritus and sleep loss on a visual analog scale (accounts for about 20% of the total score).

9.3.4 PEESS v2.0 Questionnaire

The PEESS v2.0 (Martin, 2015; Franciosi, 2011) is used to assess the frequency and severity of EoE symptoms in the last month and will be administered only for subjects with GI adverse events of interest (Section 5.5.1, Section 8.5.6.2). The PEESS v2.0 consists of 4 domains (dysphagia, GERD, nausea/vomiting, and pain) and 20 items. Each item contains response options from 0 to 4. A higher total or domain score indicates more frequent and/or severe symptoms. The parent/caregiver completes the Parent Report and subjects aged ≥ 8 years complete the Children and Teens Report.

The PEESS v2.0 was not designed to establish a diagnosis of EoE; the use of this questionnaire to monitor the clinical course of GI symptoms must be considered exploratory. However, the PEESS v2.0 has shown content and construct validity (Martin, 2015; Franciosi, 2011) and is a promising tool for following the clinical course of EoE or an EoE-like immune-mediated GI syndrome. The questionnaire has the potential to reveal trends toward symptomatic improvement or worsening that may otherwise go undetected.

9.3.5 Physical Examinations and Vital Signs

The investigator will perform physical examinations according to the schedule of activities.

Physical examinations will include an age-appropriate assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, GI, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. Symptom-directed physical examinations will concentrate on typical target organ areas for an allergic response, including the skin, oropharynx, and upper and lower respiratory, GI, and cardiovascular systems.

Vital sign measurements will include blood pressure, heart rate, and temperature.

Weight and height will be measured at specific visits according to the schedule of activities.

10 STATISTICAL METHODS

10.1 Statistical and Analytical Plans

The statistical methods and data presentations for reporting the study results will be described in detail in the statistical analysis plan.

Randomization will be central and treatment allocation will be 2:1 (AR101 treatment or standard of care alone). Randomization will be stratified by age group (4-12 years and 13-17 years).

Data for demographic and baseline characteristics, HRQOL scores, efficacy, and safety will be summarized by treatment group (AR101 treatment vs standard of care alone). Summary statistics will include the mean, number of observations, standard deviation, median, minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables.

Statistical significance is defined as $p < 0.05$ and tests will be 2-sided, unless otherwise specified. CIs will be calculated at the 95% level, reflecting a type I error rate of 0.05.

Missing values for efficacy variables will not be replaced or imputed; no interpolation or extrapolation will be applied to missing values.

10.2 Analysis Populations

The ITT population (ie, full analysis set) will be defined as all subjects who receive any part of 1 dose of study product and complete 1 study visit if assigned to AR101 treatment, or who complete 1 study visit after the screening visit if assigned to standard of care alone. The ITT population will be used for all HRQOL and efficacy analyses unless otherwise specified, and analyzed according to randomized treatment. If no subjects receive the incorrect treatment, the ITT population will be the same as the safety population.

The AR101 completer population will be defined as all AR101-treated subjects in the ITT population who complete the exit visit (ie, do not discontinue early). The standard of care completer population will be defined as all subjects in the ITT population receiving standard

of care alone who complete the OLFC after 12 months of observation and who complete the exit visit.

The AR101 per protocol population may be defined if it is sufficiently different from the AR101 completer population. The AR101 per protocol population will include all subjects in the AR101 completer population who have no major protocol deviations. The standard of care per protocol population will be defined as all subjects in the standard of care completer population who have no major protocol deviations.

The safety population will be defined as all subjects who receive any randomized study treatment (ie, who receive any part of 1 dose of study product and complete 1 study visit if assigned to AR101 treatment or who complete 1 study visit after the screening visit if assigned to standard of care alone). The safety population will be used for all safety analyses and analyzed according to treatment received.

10.3 Determination of Sample Size

This study will use multiple HRQOL questionnaires to assess changes across time in the HRQOL of subjects receiving AR101 treatment versus standard of care alone, and their parents/caregivers.

The sample size for this study is based on estimates for the FAQLQ-PF. A sample size of 144 subjects randomly assigned in a ratio of 2:1 to AR101 treatment (96 subjects) or standard of care alone (48 subjects) provides at least 80% power to detect a treatment difference of 0.75 in the adjusted mean total FAQLQ-PF scores at 18 months. The sample size calculation is based on an alpha of 0.05 and tests are assumed to be 2-sided. The common standard deviation is assumed to be 1.5 (DunnGalvin, 2010). Approximately 25% of subjects are estimated to drop out or discontinue early from the study. Therefore, approximately 200 subjects (134, AR101 treatment; 67, standard of care alone) will be randomly assigned to study treatment.

10.4 Interim Analyses

No interim analyses are planned.

10.5 Analyses of HRQOL

The primary objective assesses HRQOL of subjects receiving AR101 treatment versus standard of care alone for approximately 18 months.

No single endpoint is specified as primary because the study is not designed or intended to support a labelling claim.

The primary analyses will be on a family of proxy- and self-reported disease-specific HRQOL measures that assess the HRQOL of the peanut-allergic subject. The ITT population will be used for these analyses. Data summaries will be presented across time and accompanied by inferential analyses.

The relevant disease-specific HRQOL questionnaires (FAQLQ-PF, FAQLQ-PFT, FAQLQ-CF, FAQLQ-TF, FAIM-PF, FAIM-PFT, FAIM-CF, and FAIM-TF) are described in Sections 9.1.1 and 9.1.2.

As the number of items and domains vary by instrument, the exact algorithms used to calculate the total and domain scores, where defined, and the rules for handling missing data will be described in the statistical analysis plan. Missing data for follow-up questionnaires completed after early discontinuation will not preclude the execution of the primary analyses. Data will also be summarized separately by age group as appropriate for the questionnaire evaluated.

Descriptive statistics for the FAQLQ-PF questionnaire, completed by the parent/caregiver of subjects aged 4 to 12 years, will be presented for the total score, domain scores, individual questions, and changes from baseline across time.

As a supporting analysis, analysis of covariance (ANCOVA) will be performed on the ITT population to assess the change from baseline in the total FAQLQ-PF score and each of the domain scores at study exit (approximately 18 months). Adjustment will be made for treatment and country as main effects; baseline score will be fitted as a covariate.

The least squares mean of the treatment differences for AR101 treatment versus standard of care alone will be presented together with the corresponding 2-sided 95% CI and p-value.

The null (H_0) and alternative (H_1) hypotheses for these analyses (ie, total FAQLQ-PF score and each domain score) are as follows:

- H_0: there is no difference between groups in the mean change from baseline for AR101 treatment and standard of care alone
- H_1: there is a difference between groups in the mean change from baseline for AR101 treatment and standard of care alone

Such that:

H_0 $\mu_{AR101} = \mu_{\text{standard of care alone}}$

H_1 $\mu_{AR101} \neq \mu_{\text{standard of care alone}}$

where μ_{AR101} is estimated by the mean change from baseline from the ANCOVA in the AR101 treatment group and $\mu_{\text{standard of care alone}}$ by the mean change from baseline from the ANCOVA in the standard of care alone group

These analyses may be repeated for the completer population and the per protocol population (if defined).

Similar data presentations and analyses will be provided for the other disease-specific HRQOL questionnaires (FAQLQ-PFT, FAQLQ-CF, FAQLQ-TF, FAIM-PF, FAIM-PFT, FAIM-CF, and FAIM-TF).

Full details will be provided in the statistical analysis plan.

10.6 Analysis of Other Questionnaires

Details of the analyses for other questionnaires and bespoke questions will be provided in the statistical analysis plan. Other questionnaires include the EQ-5D, FAQL-PB, HADS, and TSQM-9. Bespoke questions include global assessment of HRQOL, assessment of control of peanut allergy and confidence in managing allergic reactions, assessment of experiences related to food challenges, and assessment of experience and satisfaction with AR101 treatment at study exit.

10.7 Analysis of Efficacy

Desensitization response rates during the OLFC will be compared between treatment groups as follows:

- The proportion of subjects tolerating a single dose of 300 mg (443 mg cumulative) of peanut protein with no or mild symptoms in the OLFC after approximately 12 months of study treatment
- The proportion of subjects tolerating a single dose of 600 mg (1043 mg cumulative) of peanut protein with no or mild symptoms in the OLFC after approximately 12 months of study treatment
- The proportion of subjects tolerating a single dose of 1000 mg (2043 mg cumulative) of peanut protein with no or mild symptoms in the OLFC after approximately 12 months of study treatment

The ITT population and Fisher exact test will be used for these analyses. For each endpoint, subjects tolerating the indicated single challenge dose of peanut protein will be considered responders; subjects who do not tolerate the indicated single challenge dose of peanut protein will be considered nonresponders. Nonresponders will also include subjects who withdraw consent or discontinue early before having the OLFC, and subjects who do not reach the 300 mg/day dose or maintain a 300 mg daily dose of study product for 12 months.

Desensitization response rates and associated 95% CIs will be presented for each treatment group using exact Clopper-Pearson CIs. The 95% CI for the treatment difference (desensitization rate for AR101 treatment minus desensitization rate for standard of care alone) will be based on exact unconditional confidence limits using the score statistic.

Additional efficacy endpoints will be assessed as follows:

The maximum dose reached with no or mild symptoms at the OLFC will be assessed by tabulating the number and percentage of subjects by maximum dose at the OLFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores (row mean score differences statistic) stratified by country will be used to test for a treatment difference.

The maximum severity of symptoms occurring at each challenge dose of peanut protein during the OLFC will be assessed by tabulating the number and percentage of subjects by

maximum severity at the OLFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores (row mean score differences statistic) stratified by country will be used to test for a treatment difference.

The proportion of subjects successfully completing the RWPC with no or mild symptoms after approximately 13 months of AR101 treatment will be assessed by presenting the response rate and the associated 95% CI using an exact Clopper-Pearson CI.

The maximum severity of symptoms during the RWPC after approximately 13 months of AR101 treatment in eligible subjects who consented to the RWPC will be assessed by tabulating the number and percentage of subjects by maximum severity.

Full details will be provided in the statistical analysis plan.

10.8 Analysis of Safety

All safety analyses will be performed using the safety population. Safety data will be listed and summarized by treatment received. Descriptive statistics will be used.

Safety data will be collected from signed informed consent/assent through early discontinuation or study exit, and through at least 30 days after early discontinuation or study exit for subjects with unresolved adverse events or through at least 6 months after early discontinuation or study exit for subjects with GI adverse events of interest.

Adverse events will be classified by system organ class and coded to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be classified by severity using the CoFAR grading system for allergic reactions, EAACI guidelines for anaphylaxis, and CTCAE for all other adverse events (Section 8.4).

Summaries of the safety of AR101 treatment and standard of care alone during the study will include the following:

- Overall summary of adverse events
- Incidence of all nonserious and serious adverse events
- Incidence of adverse events by severity grade
- AR101 treatment only:
  - Incidence of adverse events during up-dosing and maintenance
  - Incidence of adverse events with onset < 90 minutes after AR101 dosing at the study site
  - Incidence and severity of treatment-related adverse events
  - Incidence of treatment-related adverse events during up-dosing and maintenance
  - Incidence of treatment-related adverse events with onset < 90 minutes after AR101 dosing at the study site

  - Incidence of dose modifications
  - Exposure-adjusted event rates for the most frequent treatment-related adverse events (ie, adverse events in ≥ 5% of the safety population)
- Exposure-adjusted event rates for the most frequent adverse events (ie, adverse events in ≥ 5% of the safety population)
- Incidence of early treatment discontinuation due to adverse events and due to chronic or recurrent GI adverse events
- Separate summaries will be presented for anaphylaxis, allergic reaction adverse events, use of epinephrine, and accidental/nonaccidental food allergen exposure

Adverse events with onset before the first dose of AR101 treatment (or on day 1 for standard of care alone) will be listed only.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Medications will be listed and summarized by Anatomical Therapeutic Chemical (ATC) classification system level 1 and preferred name.

- Prior and concomitant medications, excluding rescue medications, will be summarized separately by ATC class, preferred name, and treatment.
- Rescue medications used during screening, initial dose escalation, up-dosing, maintenance, and overall (including all rescue medications reported on the case report form) will be summarized by ATC class, preferred name, and treatment received.
- All prior, concomitant, and rescue medications will be listed by subject.

Summary statistics will be provided for the ACT, lung function data, and laboratory data if relevant. These data will also be listed by subject.

Full details for the safety analyses will be provided in the statistical analysis plan.

10.9 Other Analyses

Additional endpoints will be assessed over the course of the study as follows:

- Changes from baseline in TNSS scores in subjects with pre-existing allergic rhinitis
- Changes from baseline in SCORAD scores in subjects with pre-existing atopic dermatitis
- Changes in peanut SPT mean wheal diameters

Full details for these analyses will be provided in the statistical analysis plan.

11 STUDY COMMITTEES AND COMMUNICATIONS

As this is open-label, an internal safety monitoring committee (SMC) will be established to monitor the study for safety. The committee will meet at least quarterly to review the study safety data in accordance with the SMC charter.

12 LABORATORY REQUIREMENTS

12.1 Clinical Laboratory Tests

Clinical laboratory tests (hematology, immunology) will be performed at screening and at unscheduled visits as necessary. Samples will be stored until the specified analyses are completed and then will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A list of the required clinical laboratory tests and other evaluations is provided in Table 20. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

All clinical laboratory tests will be performed by a central laboratory unless otherwise specified. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments. A local clinical laboratory may be used to assess samples at unscheduled visits or urgent care to evaluate an adverse event. Central laboratory samples should also be obtained whenever possible during unscheduled visits. No local laboratory data will be entered into the study database.

Additional details are provided in the laboratory manual.

Table 20: Clinical Laboratory Tests

Hematology	Immunology	Other
Red blood cell count Hemoglobin Hematocrit Platelet count White blood cell count with differential (percent and absolute) • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Total immunoglobulin (Ig) E Peanut-specific IgE and components (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9)	Pregnancy test (serum at screening; urine thereafter) for all females of childbearing potential

12.2 Basophil Activation Test

Collection of blood samples for basophil activation tests will be performed according to the schedules of activities. The Bühlmann Flow CAST assay uses flow cytometry to measure CD63 upregulation, which is a marker of basophil activation in IgE-mediated responses to peanut. The assay is conducted in whole blood treated with EDTA and tested within 24 to 48 hours of collection.

13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

The sponsor must confirm that a study site is activated before an investigator enrolls subjects in the study, and the following documents must be available:

- Fully executed clinical trial agreement
- Investigator-signed protocol signature page
- Investigator-signed acknowledgment of receipt of the current investigator brochure
- EC and regulatory authority approval letter
- EC-approved informed consent and assent forms
- Additional documents as necessary per local requirements

If an investigator changes during the course of the study, the sponsor and any local regulatory authorities, as applicable, must first approve the change of investigator and the new investigator must provide the sponsor all of the relevant documents listed above.

The sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study treatment, case report forms, monitoring, serious adverse event reporting, and other relevant information.

13.1 Ethics

13.1.1 Ethics Committee

Before initiating the study, the sponsor will obtain confirmation from the EC that the EC is properly constituted and compliant with all requirements and local regulations.

The sponsor will provide the EC with all appropriate material, such as the protocol, current investigator brochure, site-specific informed consent/assent form, and other written information provided to the subjects. The study will not be initiated until the appropriate EC and regulatory authority approval is obtained in writing for all required documentation, and copies are received by the sponsor.

EC and regulatory authority approval will be obtained for any substantial protocol amendments and informed consent/assent revisions before implementing the changes. The investigator or sponsor will provide appropriate reports on the progress of the study to the

EC, per local requirements, and to the sponsor or designee in accordance with applicable local regulations.

13.1.2 Ethical Conduct of the Study

This study will be conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including current Good Clinical Practice (GCP) according to ICH guidelines, and national and international regulations and directives as appropriate. The study will be conducted under a protocol reviewed and approved by an EC and applicable regulatory authorities; the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will provide written informed consent/assent before any protocol-specific tests or evaluations are performed.

13.1.3 Subject Information and Informed Consent and Assent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH GCP, and relevant national and international/EU regulations and directives will be obtained from each subject or pediatric subject's parent/caregiver before entering the subject in this study. A properly executed age-appropriate assent form will also be obtained from each pediatric subject. Where required by local authorities, both parents must sign the consent form before a child can be enrolled in the study. The sponsor will prepare the informed consent and assent forms for submission to the EC. The EC must approve the documents before the investigator implements them. A consent/assent form will be required for subjects to participate in the optional RWPC.

The investigator will provide copies of the signed informed consent form to each subject or signed informed consent and assent forms to a subject's parent/caregiver, and will maintain the signed original documents within the subject's clinical record per local requirements. The investigator will also fully document the informed consent process in the subject's source documents.

13.1.4 Maintaining Subject Confidentiality

All reports and subject samples will be identified only by the subject ID number and year of birth to maintain subject confidentiality. Additional subject confidentiality issues are addressed in the clinical trial agreement and in the informed consent/assent form signed by each study participant or parent/legal guardian.

13.2 Data Quality Assurance

13.2.1 Data Management

Clinical data management will be performed by the sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan

will include procedures for processing the data from this study, and will describe the responsibilities of the sponsor and designee when clinical data management is provided by an external vendor. The data management plan will include a list of the standard operating procedures that apply to this study.

Adverse events and medications will be coded using MedDRA and the WHO-DD, respectively. The dictionary versions will be named in the data management plan.

13.2.2 Case Report Forms

The study will use an electronic data capture system, and a guide will be provided for completing case report forms. All case report forms are to be fully completed, reviewed, and signed by the investigator or subinvestigators listed on the Form FDA 1572 or other appropriate local regulatory authority documents.

13.2.3 Study Monitoring

The sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the investigator grants permission to the sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the case report forms, it is mandatory that sponsor representatives (eg, study monitor) have direct access to original source documents (eg, paper or electronic subject records, subject charts, and laboratory reports) needed to verify the entries on case report forms. During the review of these documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records/source documents (paper or electronic) related to the study. The study monitor will be responsible for inspecting the case report forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness and correctness of all case report form entries. The investigator agrees to cooperate with the study monitor to ensure that any problems detected during these monitoring visits are resolved.

13.2.4 Study Audits

During the study and after study completion, it is likely that one or more quality assurance audits will be conducted by the sponsor or authorized representatives, or both. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time.

13.3 Investigational Product Accountability

The investigator must maintain accurate records of all investigational product supplies received. All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines and local and national regulations require the investigator to ensure that investigational product deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor's investigational product accountability log or other sponsor-approved pharmacy log
- That investigational product is handled and stored safely and properly in accordance with the label and the study protocol
- That investigational product is only administered or dispensed to study subjects in accordance with the protocol
- That any used or unused investigational product is returned by the subject at each required visit
- That any unused investigational product is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused investigational product are followed and only after approval by the sponsor representative
- A detailed accounting of any investigational product accidentally or deliberately destroyed

Investigational product inventory and accountability records for the investigational products will be kept by the study site. Investigational product accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply investigational product to any persons except the subjects in this study.
- The investigator/pharmacist will keep the investigational products in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the investigational product label, accessible only to those authorized by the investigator to dispense these investigational products.
- The investigator/pharmacist will maintain an investigational product inventory. The inventory will include details of materials received and a clear record of when they were dispensed and to which subject.
- The investigator/pharmacist agrees to conduct a final investigational product supply inventory and to record the results of this inventory on the investigational product accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned investigational product. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

Used or unused investigational product may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after investigational product accountability has been conducted by the sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational products will be provided to the sponsor or designee upon request for review and approval before the first onsite destruction. Unused investigational product not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

13.4 Retention of Records

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized sponsor representatives, and regulatory agency inspectors upon request. A file for each subject must be maintained that includes the signed informed consent and assent forms and copies of all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Investigators must maintain all study documentation for at least 2 years following the approval of the investigational product, or until 2 years after the investigational product program is discontinued, or longer if required by local regulations. Study documentation includes but is not limited to all essential documents as defined in ICH E6 Guidelines for Good Clinical Practice. The sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local and national regulations.

13.5 Protocol Deviations

The investigators and study site staff will conduct the study in accordance with the approved protocol. Any intentional or unintentional change, divergence, or departure from the study design or procedures will be considered a protocol deviation. Protocol deviations will be documented in accordance with the study manual and may include electronic data capture or other means.

Where necessary, the investigator may deviate from the protocol to eliminate an immediate hazard to a study subject, although every effort should be made to discuss this with the sponsor medical monitor in advance.

13.6 Study Termination

The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

The sponsor reserves the right to terminate the study anytime and for any reason. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the investigational products, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice

of the termination along with the reasons to the investigator and EC/regulatory authorities as required.

If an investigator or the investigator's EC intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason for it.

14 USE OF STUDY INFORMATION AND PUBLICATION

The results of this study will be published or presented at scientific meetings in a timely, objective, and scientifically and clinically meaningful manner that is consistent with good science and industry and regulatory authority guidance, while addressing the need to protect the intellectual property of Aimmune (sponsor), regardless of the study outcome. The data generated in this clinical study are Aimmune Confidential Information and the exclusive property of the sponsor. The sponsor's written approval is required before disclosing any information related to this clinical study, and no investigator-initiated publications may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. The sponsor, in consultation with the authors, will make the final decisions on the timing of presentation of study endpoint data and the publication venues (congresses/journals).

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be detailed in the investigator's clinical study agreement.

Any formal publication of the study in which input of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local criteria (ICMJE, 2015; updated ICMJE recommendations, 2016). The sponsor does not compensate for authorship of a publication and all authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with the sponsor or related entities, including sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the sponsor's publications committee and sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

Investigators in this study agree to have their name listed as an investigator in any publication reporting results from this study, whether or not they are an author on the publication.

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication.

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16 INVESTIGATOR SIGNATURE

AIMMUNE THERAPEUTICS, INC.

Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adolescents: Real-World, Open-Label, Quality of Life Study

Signature of Agreement for ARC009 Protocol Amendment 1.0 – 11 Apr 2018

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Declaration of Helsinki (2013), principles of Good Clinical Practice as described in the 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.

Print Study Site Name	Study Site Number (if known)
Print Investigator Name	
Investigator Signature	Date

Appendix 1: Open-Label Food Challenge Procedures

An open-label food challenge (OLFC) is a procedure performed under medical supervision by feeding a test food product (peanut) in measured, increasing doses. Food allergic reactions can potentially develop and may be severe (eg, resulting in anaphylaxis). Incremental dosing may reduce the risk of severe allergic reactions by allowing the procedure to stop for medical treatment when a reaction becomes apparent. The acceptable and safe procedures for study subjects participating in an OLFC as part of this protocol are described herein; additional procedures may be required as specified in the protocol schedule of activities.

The OLFCs conducted under this protocol will follow procedures consistent with the Practical Allergy (PRACTALL) guidelines for safety, assessment, and scoring (Sampson, 2012).

The food challenge consists of peanut (defatted peanut flour mixture containing approximately 33% peanut protein [wt/wt]) mixed in a vehicle (matrix) food. The peanut flour mixture includes additional nonallergenic, powdered flavoring agents to help further mask the distinctive flavor of peanut and a small amount of oat flour. The OLFC will use the dosing schedule shown in Table 1.

Table 1: OLFC Challenge Doses

Dose Number	Peanut Protein Dose (mg)	Cumulative Peanut Protein (mg)
1	3	3
2	10	13
3	30	43
4	100	143
5	300	443
6	600	1043
7	1000	2043

OLFC, open-label food challenge.

PROCEDURES

General Safety Considerations

A study physician will supervise all OLFCs.

Personnel involved in an OLFC must be specifically trained in the management of acute allergic reactions.

All necessary medications for treatment of an allergic reaction and resuscitation equipment must be readily available, including epinephrine, oxygen, antihistamines (both H1 and H2), beta-adrenergic agonists, corticosteroids, and intravenous (IV) fluids.

PREPARATION FOR THE OLFC

Before the Day of the OLFC

Contact the subject and parent/caregiver: Study site staff should schedule the OLFC, allowing for the washout period for antihistamines, keeping in mind the difficulty for some individuals during certain times of the year (eg, peak pollen season for rhinitis), and being mindful of visit windows. Study site staff should inform the subject and parent/caregiver in advance of the scheduled OLFC to communicate the following:

- Review the events of the day (eg, study procedures, modality of the OLFC, possibility of extended observation) and address any potential problems.
- Confirm and document the appointment date and time in the subject's source documents.
- Explain that the OLFC will be rescheduled in case of illness or symptoms such as wheezing, fever, vomiting, and diarrhea; the subject and parent/caregiver are to notify the study site if such symptoms develop before the OLFC.
- Establish that the subject's other atopic diseases (eg, asthma, eczema, rhinitis) are stable.
- Instruct that the subject is to avoid antihistamines and other current medications that may affect safety or interfere with the OLFC assessment for 5 half-lives of the medication before the OLFC begins. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.
- Instruct that food and fluids (except for water and clear liquids) are to be withheld for 2 hours before the OLFC.
- Instruct the subject to withhold the dose of study product on the day of the OLFC.
- Determine the subject's preference/tolerance for the foods that may be used for the OLFC (chocolate or vanilla pudding, or applesauce). Identify foods that must not be used for masking the product tested due to allergy.

On the Day of the OLFC

1. Check the protocol schedule of activities and complete any required procedures as specified before starting the OLFC.
2. Confirm the following:
   - Subject has not administered study product.
   - Negative urine pregnancy test for all female subjects of childbearing potential.
   - No recent or active illnesses. Reschedule the OLFC if the subject is experiencing symptoms of an acute infection (eg, fever, recent nausea, vomiting, diarrhea) or any other illness that may interfere with the subject's safety or interpretation of the results. Do not conduct the OLFC if illness is suspected.
   - Control of chronic atopic diseases. Do not proceed with the OLFC if the subject is experiencing unstable or exacerbated atopic disease such as asthma, atopic dermatitis,

urticaria, or allergic rhinitis. Reschedule the OLFC and initiate appropriate actions to control disease activity in the interval.

- No recent exacerbation for asthma specifically (no rescue albuterol for 2 days, no oral steroid rescue use within 14 days).
- Avoidance of antihistamines and other medications that may affect the OLFC for 5 half-lives of the medication before the challenge day.

3. Obtain baseline vital signs (blood pressure, heart rate, temperature).
4. Perform a symptom-directed physical examination to confirm adequate baseline.
5. Obtain peak expiratory flow rate (PEFR) measurement.
   - For subject aged ≥ 6 years, make 3 attempts and document them in the subject's source documents. The PEFR must be at least 80% of the predicted value. Reschedule the OLFC if the PEFR is < 80% of the predicted value.
   - For subject aged 4 to 5 years, attempt to measure PEFR and document it in the subject's source documents (if unable to successfully obtain, record attempts and investigator assessment).
6. Place a saline lock if directed by the supervising physician for subjects considered at high risk of allergic reaction or severe reaction based on medical history.
7. Ensure rescue medications and resuscitation equipment are available and readily accessible, including epinephrine, diphenhydramine (oral, IV), cetirizine (oral), albuterol (nebulizer or as a metered dose inhaler), IV supplies and fluids, oxygen, and suction.
   - Calculate appropriate weight-based doses of emergency medications in advance for treatment of reactions.
   - Prepare an appropriate dose of epinephrine at a 1:1000 effective concentration for intramuscular use and have it readily accessible. An epinephrine auto-injector or epinephrine in ampules/vials prepared in syringes are acceptable.

PREPARATION OF OLFC MATERIAL

1. Obtain 1 packet of peanut mixture. Record the subject identification number and date on the packet.
2. Obtain a fresh, semisolid, colloid-like vehicle food (pudding or applesauce) that the subject is not allergic to.
   - 3 containers of 92 g chocolate or vanilla pudding

     or
   - 3 containers of 113 g applesauce
3. Place an empty container on a scale and tare it to zero. Shake the peanut packet before opening, then weigh out 3.08 g of peanut mixture.
4. Peel the foil lid from the vehicle food container, and spoon half of the vehicle food (including any residual from the underside of the lid) into a mixing container.
5. Pour the weighed peanut mixture over the vehicle food, and mix thoroughly with a spoon for 5 minutes.

6. Add the remainder of the vehicle food, and mix for another 5 minutes. Let stand for 2 minutes.
7. Repeat steps 3 through 6 two more times to mix a total of 3 pudding/applesauce containers.
8. Label dosing containers with challenge doses as follows: 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg.
9. For each challenge dose, place the labeled dosing container on a scale, tare it to zero, and weigh out the corresponding amounts of vehicle food blend per Table 2. Repeat for all challenge doses.
10. Stir each dose again 5 times before giving it to the subject.

Table 2: Doses of Vehicle Food Blend for OLFC

Dose Number	Peanut Protein (mg)	Pudding Blend (g)	Applesauce Blend (g)
1	3	0.29	0.35
2	10	0.95	1.16
3	30	2.85	3.48
4	100	9.51	11.61
5	300	28.53	34.83
6	600	57.05	69.65
7	1000	95.08	116.08

OLFC, open-label food challenge.

DOSING AND MONITORING DURING THE OLFC PROCEDURE

Before Each Dose of the OLFC

1. Measure and record vital signs (blood pressure, heart rate, and temperature).
2. Perform a focused physical examination, concentrating on typical target organ areas, and review vital signs.
   - The main target organ areas for an allergic response include the skin, oropharynx, and upper and lower respiratory, gastrointestinal, and cardiovascular systems.
   - Pay special attention to the subject's overall appearance and demeanor, as early signals of anaphylaxis frequently display as changes from baseline in mood, level of anxiety, or concentration. Such changes can be subtle, especially in children who may not possess adequate verbal skills to describe their psychological distress.
3. Progress to the next dose level after waiting 20 to 30 minutes if no dose-limiting symptoms or signs (physical findings) of an allergic reaction are present and the subject is willing.
4. Doses may not be repeated in this OLFC.

Signs and Symptoms During the OLFC

At each challenge dosing level, record in the subject's source documents any signs and symptoms that changed from baseline condition.

The assessing physician is responsible for determining whether the symptoms meet the criteria for dose-limiting symptoms. Suggested guidelines for the assessment of severity of specific symptoms of an allergic reaction are provided in Table 3. When multiple symptoms are present, the severity of the most severe symptom will be used to determine whether symptoms are dose-limiting and the challenge dose level is tolerated.

Table 3: Guide for Assessment of Allergic Reaction Symptom Severity by Organ System

Organ System	Mild Symptoms	Moderate Symptoms	Severe Symptoms
Skin	Limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema) or pruritus (mild, eg, causing occasional scratching)	Systemic hives (eg, numerous or widespread hives), swelling (eg, significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema	Severe generalized urticaria/angioedema/ erythema
Respiratory	Rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort	Throat tightness without hoarseness, persistent cough, wheezing without dyspnea	Laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
Gastrointestinal	Mild abdominal discomfort (including mild nausea), minor vomiting (typically a single episode), and/or a single episode of diarrhea	Persistent moderate abdominal pain/cramping/ nausea, more than a single episode of vomiting and/or diarrhea	Severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
Cardiovascular/ Neurologic	Subjective response (weak, dizzy), or tachycardia	Moderate drop in blood pressure and/or > 20% from baseline, or significant change in mental status	Cardiovascular collapse, signs of impaired circulation (unconscious)

General recommended actions for subjects experiencing allergy symptoms are as follows:

Severe symptoms: All severe allergy symptoms are dose-limiting and indicate that the current portion of the OLFC is positive.

- **Stop the OLFC, immediately initiate appropriate treatment, and closely monitor the subject**.

Moderate symptoms: Moderate allergy symptoms are considered dose-limiting with rare exceptions, and indicate that the current portion of the OLFC is positive.

- **Stop the OLFC, immediately initiate appropriate treatment, and closely monitor the subject**.

Mild symptoms: It may be difficult to predict whether mild symptoms will resolve or progress to more serious symptoms. In this situation, safety is paramount. Certainty about the outcome must be weighed against the risk to the subject. In the event of mild symptoms, the determination of tolerability and progression to the next dose in the OLFC must be based on clinical judgment.

The following general guidelines may help determine whether a dose associated with the emergence of a mild symptom or symptoms was tolerated. A dose eliciting only mild symptoms may be considered tolerated if the symptoms are characterized by the following:

- Are isolated to a single organ system
- Resolve with no pharmaceutical intervention
- Do not worsen in intensity or distribution over time
- Resolve or show definite signs of resolving in under 1 hour
- Do not include objective wheezing

An example of a mild symptom that may permit continued dosing is mild, self-limited pruritus that resolves without treatment.

However, if an allergic response to dosing is characterized by mild symptoms that do not meet all of these criteria (eg, the subject has mild symptoms occurring in 2 or more organ systems or requires treatment of any type, the symptoms show progression in severity or distribution over time, the reaction is protracted or includes objective wheezing), then the dose may be assessed as not tolerated even though the individual allergy symptoms may be mild. **Stop the OLFC and initiate appropriate treatment**.

At the physician's discretion, the intervals between doses may be extended (eg, to 35 or 40 minutes) to determine whether the observed signs and symptoms represent a worsening allergic reaction. In this case:

- Close observation is mandatory.
- Measure vital signs (blood pressure, heart rate, temperature) at least every 15- to 20-minutes postdose for the duration of the extended observation and record them in the subject's source documents.

The physician may elect to stop the OLFC due to subjective symptoms or if the subject refuses to proceed (eg, due to significant anxiety) even if no objective allergy symptoms are documented.

OLFC OUTCOMES AND TREATMENT / OBSERVATION

Negative OLFC

Release the subject if no symptoms are detected by the end of the 2-hour observation period after the last dose.

Positive OLFC

Treatment of subjects with symptoms: Treat subjects with any symptoms elicited by the OLFC per the accepted medical practices at the study site. Record all treatments administered for allergic reactions during an OLFC in the subject's source documents and on case report forms.

Following the initial treatment:

1. Repeat treatments as needed, at the discretion of the physician.
2. Monitor vital signs (blood pressure, heart rate, temperature) at least every 15 minutes until symptoms resolve, then 30 and 60 minutes after symptoms resolve, then hourly until releasing the subject.
3. Monitor pulse oximetry if laryngeal, lower respiratory, or cardiovascular symptoms are present.
4. Follow these guidelines for further observation based on symptom severity:
   - For severe symptoms, observe the subject for a minimum of 3 hours after the symptoms resolve, either at the study site or an emergency facility, as appropriate. Consider extended overnight observation if symptoms are protracted.
   - For moderate symptoms, observe the subject for a minimum of 2 hours after the symptoms resolve, and longer if necessary.
   - For mild symptoms, observe the subject for a minimum of 2 hours or for 1 hour after the symptoms resolve, whichever is longer.
5. Do not release a subject with symptoms or with abnormal vital signs if changed from baseline. As appropriate, arrange for continued observation at the study site, an emergency facility, or an extended-stay (inpatient) unit. Record signs and symptoms that changed from baseline in the subject's source documents.
6. Generally, if the emergence of allergy symptoms halts the OLFC, consider the last symptom-eliciting dose to be "not tolerated" and record it as such on the case report form.
   - Exceptions to this guidance may include situations where the OLFC is halted (eg, due to anxiety or refusal to continue) and symptoms are mild and not considered to be dose-limiting.

POST-OLFC INSTRUCTIONS AND FOLLOW-UP

Before releasing the subject, study site staff should inform the subject and parent/caregiver of the following:

1. The subject may resume eating and drinking without restrictions 30 minutes after the last OLFC dose is administered. Subjects who tolerate at least 300 mg of peanut protein at the OLFC will resume study treatment (AR101 or standard of care alone) the day after the OLFC.
2. Review the possibility of delayed allergy symptoms and provide guidance on how to recognize anaphylaxis.

3. Verify that they possess an epinephrine auto-injector with an appropriate dose and expiry date before release, and review the instructions for administration of injectable epinephrine.
4. Provide study site staff contact information and procedures for after-hours emergencies.
5. Instruct that the subject is to continue to avoid eating peanuts and foods known to contain peanuts.
6. Schedule a follow-up study appointment according to the protocol.
7. Telephone the following day to inquire about post-OLFC adverse events, and assist accordingly.

REFERENCE

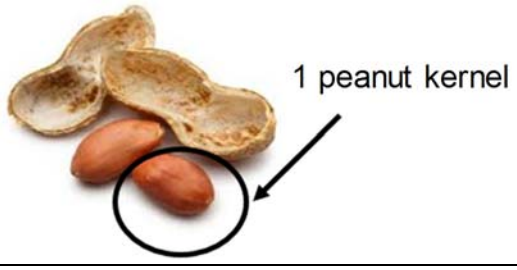
Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.

Appendix 2: Real-World Food Challenge Procedures

The real-world peanut challenge (RWPC) is designed to closely mimic an accidental exposure to peanut. While food challenges using measured, increasing doses of peanut protein are designed to assess tolerance, how such graded challenges predict outcomes to an accidental exposure is poorly understood. The acceptable and safe procedures for study subjects participating in RWPCs as part of this protocol are described herein; additional procedures may be required as specified in the protocol schedule of activities.

The RWPCs conducted under this protocol will follow procedures consistent with the Practical Allergy (PRACTALL) guidelines for safety, assessment, and scoring (Sampson, 2012). Subjects will consume a food of their choice containing 500 to 600 mg of peanut protein; examples are shown in Table 1. The study site will provide the foods used in the RWPC.

Table 1: Example Foods Containing 500 to 600 mg of Peanut Protein

Food	Amount of Food Equivalent to 500-600 mg of Peanut Protein	
Dry-roasted peanut	2 peanut kernels	
Peanut butter	0.5 teaspoon or 2.5 grams	
Peanut M&M's	2 pieces	
		

PROCEDURES

General Safety Considerations

A study physician will supervise all RWPCs.

Personnel involved in an RWPC must be specifically trained in the management of acute allergic reactions.

All necessary medications for treatment of an allergic reaction and resuscitation equipment must be readily available, including epinephrine, oxygen, antihistamines (both H1 and H2), beta-adrenergic agonists, corticosteroids, and intravenous (IV) fluids.

PREPARATION FOR THE RWPC

Before the Day of the RWPC

Determine eligibility:

- Verify that signed informed consent/assent to participate in the optional RWPC is in the subject's source documents.
- Confirm the subject completed the protocol-specified open-label food challenge (OLFC) and tolerated the 1000 mg dose without dose-limiting symptoms.

Contact the subject and parent/caregiver: Study site staff should schedule the RWPC mindful of visit windows. Study site staff should inform the subject and parent/caregiver in advance of the scheduled RWPC to communicate the following:

- Review the events of the day (eg, study procedures, modality of the RWPC, possibility of extended observation) and address any potential problems.
- Confirm and document the appointment date and time in the subject's source documents.
- Explain that the RWPC will be rescheduled in the case of illness or symptoms such as wheezing, fever, vomiting, and diarrhea; the subject or parent/caregiver is to notify the study site if such symptoms develop before the RWPC.
- Establish that the subject's other atopic diseases (eg, asthma, eczema, rhinitis) are stable.
- Instruct that the subject is to avoid antihistamines and other current medications that may affect safety or interfere with the RWPC assessment for 5 half-lives of the medication before the RWPC. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.
- Instruct the subject to continue administration of study product at the usual time.
- Confirm the subject's choice of RWPC food (Table 1) and ensure its availability at the study site.

On the Day of the RWPC

1. Check the protocol schedule of activities and complete any required procedures as specified before starting the RWPC.
2. Confirm the following:
   - No recent or active illnesses. Reschedule the RWPC if the subject is experiencing symptoms of an acute infection (eg, fever, recent nausea, vomiting, diarrhea) or any other illness that may interfere with the subject's safety or interpretation of the results. Do not conduct the RWPC if illness is suspected.

- Control of chronic atopic diseases. Do not proceed with the RWPC if the subject is experiencing unstable or exacerbated atopic disease such as asthma, atopic dermatitis, urticaria, or allergic rhinitis. Reschedule the RWPC and initiate appropriate actions to control disease activity in the interval.
- No recent exacerbation for asthma specifically (no rescue albuterol for 2 days, no oral steroid rescue use within 14 days).
- Avoidance of antihistamines and other medications that may affect the RWPC for 5 half-lives of the medication before the challenge day.

3. Obtain baseline vital signs (blood pressure, heart rate, temperature).
4. Perform a symptom-directed physical examination to confirm an adequate baseline.
5. Obtain peak expiratory flow rate (PEFR) measurement.
   - For subject aged ≥ 6 years, make 3 attempts and document them in the subject's source documents. The PEFR must be at least 80% of the predicted value or personal best. If the PEFR is < 80% of the predicted value or personal best, reschedule the RWFC.
   - For subject aged 4 to 5 years, attempt to measure PEFR and document it in the subject's source documents (if unable to successfully obtain, record attempts and investigator assessment).
6. Place a saline lock if directed by the supervising physician for subjects considered at high risk of allergic reaction or severe reaction based on medical history.
7. Ensure rescue medications and resuscitation equipment are available and readily accessible, including epinephrine, diphenhydramine (oral, IV), cetirizine (oral), albuterol (nebulizer or as a metered dose inhaler), IV supplies and fluids, oxygen, and suction.
   - Calculate appropriate weight-based doses of emergency medications in advance for treatment of reactions.
   - Prepare an appropriate dose of epinephrine at a 1:1000 effective concentration for intramuscular use and have it readily accessible. An epinephrine auto-injector or epinephrine in ampules/vials prepared in syringes are acceptable.
8. Prepare the RWFC food option (Table 1) that the subject selected for the procedure.

DOSING AND MONITORING DURING THE RWPC PROCEDURE

1. Measure and record vital signs (blood pressure, heart rate, temperature) immediately before providing the RWPC food.
2. Provide the selected food and instruct the subject to completely consume it within a 10-minute period.
3. Monitor for signs and symptoms of an allergic reaction for a minimum of 2 hours after the subject fully consumes the food. Measure vital signs (blood pressure, heart rate, temperature) approximately every 30 minutes and assess for signs or symptoms of an allergic reaction.

RWPC OUTCOMES AND TREATMENT / OBSERVATION

Negative RWPC

Release the subject if no symptoms are detected by the end of the 2-hour observation period.

Positive RWPC

Treatment of subjects with symptoms: Treat subjects with any symptoms elicited by the RWPC per the accepted medical practices at the study site. Record all treatments administered for allergic reactions in the subject's source documents and on case report forms.

1. Assess the symptom severity and extend the monitoring period as appropriate. The severity of the reaction will be determined based on the investigator's judgment. Definitions of allergic symptom severity are provided as a general guide in Table 2. These definitions were developed consistent with the PRACTALL consensus report.
2. Following the initial treatment, repeat treatments as needed, at the discretion of the physician.
3. Monitor vital signs (blood pressure, heart rate, temperature) at least every 15 minutes until symptoms resolve, then 30 and 60 minutes after symptoms resolve, then hourly until releasing the subject.
4. Monitor pulse oximetry if laryngeal, lower respiratory, or cardiovascular symptoms are present.
5. Follow these guidelines for further observation based on symptom severity:
   - For severe symptoms, observe the subject for a minimum of 3 hours after the symptoms resolve, either at the study site or an emergency facility, as appropriate. Consider extended overnight observation if symptoms are protracted.
   - For moderate symptoms, observe the subject for a minimum of 2 hours after the symptoms resolve, and longer if necessary.
   - For mild symptoms, observe the subject for a minimum of 2 hours or for 1 hour after the symptoms resolve, whichever is longer.
6. Do not release a subject with symptoms or with abnormal vital signs if changed from baseline. As appropriate, arrange for continued observation at the study site, an emergency facility, or an extended-stay (inpatient) unit. Record signs and symptoms that changed from baseline in the subject's source documents.

Table 2: Guide for Assessment of Allergic Reaction Symptom Severity by Organ System

Organ System	Mild Symptoms	Moderate Symptoms	Severe Symptoms
Skin	Limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema) or pruritus (mild, eg, causing occasional scratching)	Systemic hives (eg, numerous or widespread hives), swelling (eg, significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema	Severe generalized urticaria/angioedema/ erythema
Respiratory	Rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort	Throat tightness without hoarseness, persistent cough, wheezing without dyspnea	Laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
Gastrointestinal	Mild abdominal discomfort (including mild nausea), minor vomiting (typically a single episode), and/or a single episode of diarrhea	Persistent moderate abdominal pain/cramping/ nausea, more than a single episode of vomiting and/or diarrhea	Severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
Cardiovascular/ Neurologic	Subjective response (weak, dizzy), or tachycardia	Moderate drop in blood pressure and/or > 20% from baseline, or significant change in mental status	Cardiovascular collapse, signs of impaired circulation (unconscious)

POST-RWPC INSTRUCTIONS AND FOLLOW-UP

Before releasing the subject, study site staff should inform the subject and parent/caregiver of the following:

1. The subject may resume eating and drinking without restrictions 30 minutes after the RWPC food is completely consumed. Subjects who complete the RWPC (regardless of the outcome) will continue daily maintenance treatment with study product.
2. Review the possibility of delayed allergy symptoms and provide guidance on how to recognize anaphylaxis.
3. Verify that they possess an epinephrine auto-injector with an appropriate dose and expiry date before release, and review the instructions for administration of injectable epinephrine.
4. Provide study site staff contact information and procedures for after-hours emergencies.
5. Instruct that the subject is to continue to avoid eating peanuts and foods known to contain peanuts.
6. Schedule a follow-up study appointment according to the protocol.
7. Telephone the following day to inquire about post-RWPC adverse events, and assist accordingly.

REFERENCE

Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.

Appendix 3: Study Schedule of Activities for All Subjects: Screening (Days -28 to -1)

Activity	Comments
General	Complete screening procedures within 28 days after obtaining signed consent.
Informed consent, screening number	Obtain consent (and assent if applicable) before performing any study-specific procedures. Ensure consent is on current version of form reviewed by the ethics committee.
Demographics, medical history	Includes allergy history (including anaphylactic reactions) and symptoms, diet/food allergen history, and proxy- and self-reported severity of peanut allergy. Also includes family history of peanut and other food allergy.
Weight, height	
Vital signs	Measure blood pressure, heart rate, and temperature.
ACT/C-ACT, SCORAD, TNSS	For subject with asthma: ACT for subject aged ≥ 12 years; C-ACT for subject aged 4-11 years and parent/caregiver. For subject with atopic dermatitis: SCORAD. For subject with allergic rhinitis: TNSS (short form).
PEFR and/or spirometry (FEV_1)	For subject aged ≥ 6 years, obtain PEFR; record the best result of 3 attempts. For subject with asthma, obtain spirometry (FEV_1); record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment). For subject aged 4-5 years, obtain PEFR; record results (if unable to successfully obtain, record attempts and investigator assessment). Reliable performance is not required for study eligibility at the discretion of the investigator.
Asthma evaluation	For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria (Table 19).
Food allergy instruction	Provide food/peanut allergy education (including recognition of an allergic reaction, symptoms of anaphylaxis, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to peanut) per standard of care at the study site. Verify that subject has an epinephrine auto-injector, including appropriate dose and expiry. Instruct subject to avoid peanut during the study. Document the discussion in the subject's source records.
Physical examination	Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
Pretreatment adverse event review	Record adverse event information (including allergy symptoms) from the time of signed informed consent/assent.
Concomitant medications review & instruction	Record all medications taken within 90 days before screening. Instruct subject to discontinue antihistamines at least 5 half-lives of the medication before the skin prick test and randomization. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.
Skin prick test	Measure wheal diameter for peanut extract.
Laboratory Evaluations (Central)	Refer to the laboratory manual for sample collection and processing.
Hematology, immunology	Complete blood count with differential. Total, peanut-specific, and peanut component-specific IgE.
Serum pregnancy test	For all females of childbearing potential.

Activity	Comments
Blood sample for basophil activation test (BAT)	
Eligibility Confirmation	
Eligibility confirmation	Confirm eligibility after completion of all screening activities. After confirmation of eligibility, randomization must not occur until after completion of baseline questionnaires per Appendix 4 and Appendix 6.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; FEV_1, forced expiratory volume in the first second of expiration; Ig, immunoglobulin; NHLBI, National Heart, Lung, and Blood Institute; PEFR, peak expiratory flow rate; SCORAD, scoring atopic dermatitis; TNSS, Total Nasal Symptom Score.

Appendix 4: Study Schedule of Activities for AR101 Treatment: Initial Dose Escalation and Up-Dosing

Study Period	Initial Dose Escalation		Up-Dosing				Early
Study Visit	Day 1 [1]	Day 2 [2]	At Study Site	At 80 mg	At 300 mg	Unsched [3]	Disc [4]
Interval	na	na	Every 2 weeks	Varies	Varies	Varies	Varies
Window (Days)	na	na	±3	±3	±3	na	±3
HRQOL Questionnaires and Bespoke Questions [5]							
EQ-5D [6]	X			X	X		X [7]
FAQL-PB [8]	X						X
HADS [8]	X						X
FAQLQ, FAIM [9]	X			X	X		X [7]
Bespoke global assessment of HRQOL	X						X
Bespoke assessment of control and confidence	X						X
Randomization	X						
General Activities							
Weight, height	X	X	X	X	X	X	X
Vital signs (blood pressure, heart rate, temperature)	X	X	X	X	X	X	X
ACT/C-ACT, SCORAD, TNSS (if completed at screening)				X	X	X (optional)	X
PEFR [10]	X	X	X	X	X	X (optional)	X
Asthma evaluation [11]				X	X	X (optional)	X
Symptom-directed physical examination [12]		X	X			X	
Complete physical examination [12]	X			X	X	X (optional)	X
Diet/food allergen exposure review	X	X	X	X	X	X	X
Food allergy instruction [13]	X	X	X	X	X	X (optional)	X
Contraception review	X	X	X	X	X	X (optional)	
Adverse events review [14]	X	X	X	X	X	X	X
Concomitant medications review & instruction [15]	X	X	X	X	X	X	X
Study product administration [16]	X	X	X	X	X	X (optional)	
Study product dispensing [17]		X	X	X	X	X (optional)	
Study product accountability			X	X	X	X (optional)	X
Telephone call [18]		X	X	X	X	X (optional)	

Study Period	Initial Dose Escalation		Up-Dosing				Early
Study Visit	Day 1 [1]	Day 2 [2]	At Study Site	At 80 mg	At 300 mg	Unsched [3]	Disc [4]
Interval	na	na	Every 2 weeks	Varies	Varies	Varies	Varies
Window (Days)	na	na	±3	±3	±3	na	±3
Laboratory Evaluations [19]							
Urine pregnancy test [20]				X	X	X (optional)	X
Blood sample for basophil activation test (BAT)							X

[1] Day 1 HRQOL questionnaires and bespoke questions are to be administered after eligibility is confirmed and must be completed before randomization. Day 1 activities must begin within 28 days after obtaining signed consent/assent and should be the same day as randomization (within 3 days after randomization only if the same day is not feasible). The timing of day 1 study product administration, vital signs, and assessment of allergic reactions for initial dose escalation is presented in Table 3.

[2] Day 2 should be the next consecutive day after day 1. If circumstances (eg, an intercurrent illness) create a safety risk, day 2 may be delayed up to 7 days after day 1.

[3] Anytime necessary to assess or follow up adverse events, at the subject's request, or per investigator decision. Perform procedures, spirometry, and laboratory tests as appropriate.

[4] For subject unable to complete initial dose escalation or up-dosing; approximately 14 days after the last dose.

[5] Instruct subject and parent/caregiver to complete HRQOL questionnaires and bespoke questions at the start of the visit before other procedures (unless specified otherwise). The same parent/caregiver should complete all relevant questionnaires during the study.
For age-relevant questionnaires, subject who transitions from one age group to the next age group during the study will complete the version first used.

[6] Parent/caregiver: EQ-5D-5L, EQ-5D-Y proxy (for subject aged 4-7 years); subject aged 8-12 years: EQ-5D-Y; subject aged 13-17 years: EQ-5D-5L. In addition, instruct subject and parent/caregiver to complete the questionnaire as follows:
- Before leaving the study site if severe dose-related allergy symptoms occur during an up-dosing visit (Section 8.5.1), and 1 week later.
- When allergy symptoms due to study product or food allergen exposure are reported to the study site and assessed as severe (Section 8.5.6.3), and 1 week later.

[7] Subject discontinuing before the start of maintenance: Subject and parent/caregiver will complete relevant EQ-5D, FAQLQ, and FAIM questionnaires at early discontinuation and 12 and 18 months after day 1.

[8] For parent/caregiver.

[9] Parent/caregiver of subject aged ≤ 12 years: FAQLQ-PF and FAIM-PF; parent/caregiver of subject aged 13-17 years: FAQLQ-PFT and FAIM-PFT; subject aged 8-12 years: FAQLQ-CF and FAIM-CF; subject aged 13-17 years: FAQLQ-TF and FAIM-TF.

[10] For subject aged ≥ 6 years, obtain PEFR at approximately the same time of day for each assessment visit (eg, morning, afternoon); record the best result of 3 attempts. Obtain spirometry (FEV_1) if PEFR shows a clinically relevant reduction, subject has clinical deterioration (eg, active wheeze on physical examination), or as clinically indicated at unscheduled visits; record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment).
For subject aged 4-5 years, obtain PEFR; record results (if unable to successfully obtain, record attempts and investigator assessment).

[11] For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria (Table 19).

[12] Symptom-directed: Assess systems per standard of care at the study site or as clinically indicated by symptoms.
Complete: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).

[13] Instruct subject to avoid peanut during the study. Provide food/peanut allergy education (including recognition of an allergic reaction, symptoms of anaphylaxis, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to peanut) per standard of care at the study site.

[14] For subject with GI adverse events of interest (Section 8.5.6.2), instruct subject aged ≥ 8 years and parent/caregiver to complete the PEESS v2.0 questionnaire while subject is symptomatic, at early discontinuation or study exit, and during safety follow-up.
Subject with unresolved adverse events at early discontinuation will have safety follow-up per Appendix 7.

[15] Review medications since previous visit. Instruct subject to discontinue antihistamines at least 5 half-lives of the medication before initial dose-escalation day 1. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.

[16] Administer study product at the study site per the dose-escalation schedule (up-dosing, Table 4) and dose modification guidelines (Section 8.5.3). Measure blood pressure and heart rate and assess signs/symptoms of allergic reaction at 15-30 minutes postdose and every 30 minutes thereafter until 90 minutes postdose or end of observations for allergy symptoms, whichever is last.

[17] Review instructions for administration of study product at home. Instruct that subject withhold study product when it will be administered at the study site.

[18] On the day after day 2 and the day after up-dosing visits: Contact subject and parent/caregiver by telephone for adverse events review and to inquire about compliance with study product dosing.

[19] Refer to the laboratory manual for sample collection and processing.

[20] For all females of childbearing potential.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; disc, discontinuation; EQ-5D, European Quality of Life 5-Dimensions health questionnaire; EQ-5D-5L, EQ-5D 5-Levels; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; FEV_1, forced expiratory volume in the first second of expiration; GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; na, not applicable; NHLBI, National Heart, Lung, and Blood Institute; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0; PEFR, peak expiratory flow rate; SCORAD, scoring atopic dermatitis; TNSS, Total Nasal Symptom Score.

Appendix 5: Study Schedule of Activities for AR101 Treatment: Maintenance

Study Period	Maintenance										Unsched [1]	ED [2]	Exit [2]
Study Visit (Week)	1, 5, 9	13	17, 21	25	OLFC [3]	RWPC [4]	29	33, 37	41	45, 49	na	na	53
Interval	Every 4 weeks										Varies	Varies	na
Window (Days)	±7										na	±3	±7
HRQOL Questionnaires and Bespoke Questions [5]													
EQ-5D [6]		X			X [6]	X [6]			X			X [7]	X
FAQL-PB [8]		X							X			X	X
HADS [8]		X							X			X	X
FAQLQ, FAIM [9]		X			X [9]	X [9]			X			X [7]	X
Bespoke global assessment of HRQOL		X							X			X	X
Bespoke assessment of control and confidence		X							X			X	X
Bespoke assessment of food challenge outcomes					X [10]	X [10]							
TSQM-9												X	X
Bespoke exit questionnaire												X	X
Exit interview [11]												X	X
General Activities													
Weight, height	X	X	X	X			X	X	X	X	X	X	X
Vital signs (blood pressure, heart rate, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X
ACT/C-ACT, SCORAD, TNSS (if completed at screening)		X			X	X			X		X (optional)	X	X
PEFR [12]	X	X	X	X	X	X	X	X	X	X	X (optional)	X	X
Asthma evaluation [13]		X			X	X			X		X (optional)	X	X
Symptom-directed physical examination [14]	X	X	X	X	X	X	X	X	X	X	X		
Complete physical examination [14]											X (optional)	X	X
Diet/food allergen exposure review	X	X	X	X			X	X	X	X	X	X	X
Food allergy instruction [15]	X	X	X	X			X	X	X	X	X (optional)	X	X
Contraception review	X	X	X	X			X	X	X	X	X (optional)		
Adverse events review [16]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review & instruction [17]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study product administration [18]	X	X	X	X			X	X	X	X	X (optional)		

Study Period	Maintenance										Unsched [1]	ED [2]	Exit [2]
Study Visit (Week)	1, 5, 9	13	17, 21	25	OLFC [3]	RWPC [4]	29	33, 37	41	45, 49	na	na	53
Interval	Every 4 weeks										Varies	Varies	na
Window (Days)	±7										na	±3	±7
Study product dispensing [19]	X	X	X	X			X	X	X	X	X (optional)		
Study product accountability	X	X	X	X			X	X	X	X	X (optional)	X	X
Skin prick test to peanut extract					X [20]								
OLFC [3]					X								
Optional RWPC [4]						X							
Telephone call [21]	X	X	X	X	X	X	X	X	X	X	X (optional)		
Laboratory Evaluations [22]													
Urine pregnancy test [23]					X [20]						X (optional)	X	X
Blood sample for basophil activation test (BAT)					X [20]							X	X

[1] Anytime necessary to assess or follow up adverse events, at the subject's request, or per investigator decision. Perform procedures, spirometry, and laboratory tests as appropriate.

[2] Early discontinuation: For subject who discontinues treatment early; approximately 14 days after the last dose.
Exit: For subject who receives 300 mg/day maintenance for approximately 12 months.

[3] Perform OLFC after at least 6 months (up to 7 months) of maintenance (ie, week 27 up to week 31) with AR101 at 300 mg/day.

[4] For subject who tolerates 1000 mg of peanut protein (2043 mg cumulative) at the OLFC and consents to the optional RWPC. Perform RWPC within 4 weeks (preferably within 1 week) after the OLFC.

[5] Instruct subject and parent/caregiver to complete HRQOL questionnaires and bespoke questions at the start of the visit before other procedures (unless specified otherwise). The same parent/caregiver should complete all relevant questionnaires during the study.
For age-relevant questionnaires, subject who transitions from one age group to the next age group during the study will complete the version first used.

[6] Parent/caregiver: EQ-5D-5L, EQ-5D-Y proxy (for subject aged 4-7 years); subject aged 8-12 years: EQ-5D-Y; subject aged 13-17 years: EQ-5D-5L.
In addition, instruct subject and parent/caregiver to complete the questionnaire as follows:

- Before the OLFC and optional RWPC.
- When allergy symptoms due to study product or food allergen exposure are reported to the study site and assessed as severe (Section 8.5.6.3), and 1 week later.

[7] Subject discontinuing after completing less than 9 months of maintenance (ie, between maintenance visit week 1 and 41): Subject and parent/caregiver will complete relevant EQ-5D, FAQLQ, and FAIM questionnaires at early discontinuation and 18 months after day 1.

[8] For parent/caregiver.

[9] Parent/caregiver of subject aged ≤ 12 years: FAQLQ-PF and FAIM-PF; parent/caregiver of subject aged 13-17 years: FAQLQ-PFT and FAIM-PFT; subject aged 8-12 years: FAQLQ-CF and FAIM-CF; subject aged 13-17 years: FAQLQ-TF and FAIM-TF.
Instruct subject and parent/caregiver to complete the FAQLQ/FAIM before the OLFC and optional RWPC.

[10] Instruct subject aged ≥ 13 years and parent/caregiver to complete questionnaires after the end of the observation period for the food challenge (OLFC or optional RWPC) and after the results are explained.

[11] Conduct in a random sample of parents/caregivers and subjects aged ≥ 13 years.

[12] For subject aged ≥ 6 years, obtain PEFR at approximately the same time of day for each assessment visit (eg, morning, afternoon); record the best result of 3 attempts. Obtain spirometry (FEV_1) if PEFR shows a clinically relevant reduction, subject has clinical deterioration (eg, active wheeze on physical examination), or as clinically indicated at unscheduled visits; record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment).
For subject aged 4-5 years, obtain PEFR; record results (if unable to successfully obtain, record attempts and investigator assessment).

[13] For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria (Table 19).

[14] Symptom-directed: Assess systems per standard of care at the study site or as clinically indicated by symptoms.
Complete: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).

[15] Instruct subject to avoid peanut during the study. Provide food/peanut allergy education (including recognition of an allergic reaction, symptoms of anaphylaxis, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to peanut) per standard of care at the study site.

[16] For subject with GI adverse events of interest (Section 8.5.6.2), instruct subject aged ≥ 8 years and parent/caregiver to complete the PEESS v2.0 questionnaire while subject is symptomatic, at early discontinuation or study exit, and during safety follow-up.
Subject with unresolved adverse events at early discontinuation or study exit will have safety follow-up per Appendix 7.

[17] Review medications since previous visit. Instruct subject to discontinue antihistamines at least 5 half-lives of the medication before the skin prick test, OLFC, and optional RWPC. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.

[18] Administer study product at the study site per dose modification guidelines (Section 8.5.3), except on the day of the OLFC. Measure blood pressure and heart rate and assess signs/symptoms of allergic reaction at 15-30 minutes postdose and every 30 minutes thereafter until at least 90 minutes postdose or the end of the observation period, whichever is last. The postdose observation period may be shortened to 30 minutes during maintenance if no allergy symptoms occurred during the previous 3 maintenance visits.

[19] Review instructions for administration of study product at home. Instruct that subject withhold study product when it will be administered at the study site and on the day of the OLFC.

[20] Perform before the OLFC.

[21] On the day after maintenance visits, OLFC, and optional RWPC: Contact subject and parent/caregiver by telephone for adverse events review and to inquire about compliance with study product dosing.

[22] Refer to the laboratory manual for sample collection and processing.

[23] For all females of childbearing potential.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; ED, early discontinuation; EQ-5D, European Quality of Life 5-Dimensions health questionnaire; EQ-5D-5L, EQ-5D 5-Levels; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; FEV_1, forced expiratory volume in the first second of expiration; GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; na, not applicable; NHLBI, National Heart, Lung, and Blood Institute; OLFC, open-label food challenge; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0; PEFR, peak expiratory flow rate; RWPC, real-world peanut challenge; SCORAD, scoring atopic dermatitis; TNSS, Total Nasal Symptom Score; TSQM-9, Treatment Satisfaction Questionnaire for Medication; unsched, unscheduled.

Appendix 6: Study Schedule of Activities for Standard of Care Alone

Study Visit (Week)	1	14	27	40	OLFC / 53	66	Unsched [1]	Early Disc [2]	Exit / 79 [2]
Window (Days)	na	±7					na	na	±7
HRQOL Questionnaires and Bespoke Questions [3]									
EQ-5D [4]	X	X	X	X	X [4]	X		X	X
FAQL-PB [5]	X			X		X		X	X
HADS [5]	X			X		X		X	X
FAQLQ, FAIM [6]	X	X	X	X	X [6]	X		X	X
Bespoke global assessment of HRQOL	X			X		X		X	X
Bespoke assessment of control and confidence	X			X		X		X	X
Assessment of food challenge outcomes					X				
Randomization [7]	X								
General Activities									
Weight, height	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, heart rate, temperature)	X	X	X	X	X	X	X	X	X
ACT/C-ACT, SCORAD, TNSS (if completed at screening)		X	X	X	X	X	X (optional)	X	X
PEFR [8]	X	X	X	X	X	X	X (optional)	X	X
Asthma evaluation [9]		X	X	X	X	X	X (optional)	X	X
Symptom-directed physical examination [10]		X	X	X	X	X	X		
Complete physical examination [10]	X						X (optional)	X	X
Diet/food allergen exposure review	X	X	X	X	X	X	X	X	X
Food allergy instruction [11]	X	X	X	X	X	X	X (optional)	X	X
Contraception review	X	X	X	X	X	X	X (optional)		
Adverse events review [12]	X	X	X	X	X	X	X	X	X
Concomitant medications review & instruction [13]	X	X	X	X	X	X	X	X	X
Skin prick test to peanut extract					X [14]				
OLFC					X [15]				
Laboratory Evaluations [16]									
Urine pregnancy test [17]			X		X [14]		X (optional)	X	X
Blood sample for basophil activation test (BAT)					X [14]			X	X

[1] Anytime necessary to assess or follow up adverse events, at the subject's request, or per investigator decision. Perform procedures, spirometry, and laboratory tests as appropriate.

[2] Early discontinuation: For subject who discontinues observation early.
Exit: Approximately 18 months after randomization.

[3] Instruct subject and parent/caregiver to complete HRQOL questionnaires and bespoke questions at the start of the visit before other procedures (unless specified otherwise). The same parent/caregiver should complete all relevant questionnaires during the study.
For age-relevant questionnaires, subject who transitions from one age group to the next age group during the study will complete the version first used.

[4] Parent/caregiver: EQ-5D-5L, EQ-5D-Y proxy (for subject aged 4-7 years); subject aged 8-12 years: EQ-5D-Y; subject aged 13-17 years: EQ-5D-5L.
In addition, instruct subject and parent/caregiver to complete the questionnaire as follows:
- Before the OLFC.
- When allergy symptoms due to food allergen exposure are reported to the study site and assessed as severe (Section 8.5.6.3), and 1 week later.

[5] For parent/caregiver.

[6] Parent/caregiver of subject aged ≤ 12 years: FAQLQ-PF and FAIM-PF; parent/caregiver of subject aged 13-17 years: FAQLQ-PFT and FAIM-PFT; subject aged 8-12 years: FAQLQ-CF and FAIM-CF; subject aged 13-17 years: FAQLQ-TF and FAIM-TF.
Instruct subject and parent/caregiver to complete the FAQLQ/FAIM before the OLFC.

[7] Day 1 of standard of care alone is the day of randomization, which must begin within 28 days after obtaining signed consent.

[8] For subject aged ≥ 6 years, obtain PEFR at approximately the same time of day for each assessment visit (eg, morning, afternoon); record the best result of 3 attempts. Obtain spirometry (FEV_1) if PEFR shows a clinically relevant reduction, subject has clinical deterioration (eg, active wheeze on physical examination), or as clinically indicated on unscheduled visits; record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment).
For subject aged 4-5 years, obtain PEFR; record results (if unable to successfully obtain, record attempts and investigator assessment).

[9] For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria (Table 19).

[10] Symptom-directed: Assess systems per standard of care at the study site or as clinically indicated by symptoms.
Complete: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).

[11] Instruct subject to avoid peanut during the study. Provide food/peanut allergy education (including recognition of an allergic reaction, symptoms of anaphylaxis, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to peanut) per standard of care at the study site.

[12] Subject with unresolved adverse events at early discontinuation or study exit will have safety follow-up per Appendix 7.

[13] Review medications since previous visit. Instruct subject to discontinue antihistamines at least 5 half-lives of the medication before the OLFC. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.

[14] Perform before the OLFC.

[15] Approximately 12 months (+1 month) after randomization. On the day after, phone subject for adverse event review.

[16] Refer to the laboratory manual for sample collection and processing.

[17] For all females of childbearing potential.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; disc, discontinuation; EQ-5D, European Quality of Life 5-Dimensions health questionnaire; EQ-5D-5L, EQ-5D 5-Levels; EQ-5D-Y, EQ-5D Youth; FAIM, Food Allergy Independent Measure; FAIM-CF, FAIM - child form; FAIM-PF, FAIM - parent form; FAIM-PFT, FAIM - parent form teenager; FAIM-TF, FAIM - teenager form; FAQL-PB, Food Allergy Quality of Life - Parental Burden; FAQLQ, Food Allergy Quality of Life Questionnaire; FAQLQ-CF, FAQLQ - child form; FAQLQ-PF, FAQLQ - parent form; FAQLQ-PFT, FAQLQ - parent form teenager; FAQLQ-TF, FAQLQ - teenager form; FEV_1, forced expiratory volume in in the first second of expiration; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; na, not applicable; NHLBI, National Heart, Lung, and Blood Institute; OLFC, open-label food challenge; PEFR, peak expiratory flow rate; SCORAD, scoring atopic dermatitis; TNSS, Total Nasal Symptom Score; unsched, unscheduled.

Appendix 7: Study Schedule of Activities for Subjects Who Discontinue Treatment Early or Exit With Ongoing Adverse Event: Safety Follow-Up

Activity	Safety Follow-Up	Comments
General		Follow-up is for ongoing adverse events until they resolve or stabilize (for at least 30 days after early discontinuation or exit), or consent for follow-up is withdrawn, or the study is terminated. For subject who discontinued due to GI adverse events (Section 8.5.6.2), follow-up at the study site is monthly for 6 months or until chronic or recurrent GI symptoms resolve or stabilize, whichever is last.
Adverse events review	X	Telephone subject who does not come to the study site.
Symptom-directed physical examination	X	For subject who discontinued due to GI adverse events. Assess systems per standard of care at the study site or as clinically indicated by symptoms. Telephone follow-up by medically qualified personnel may be appropriate in the absence of symptoms, at the discretion of the investigator.
PEESS v2.0 questionnaire	X	Instruct subject who had GI adverse events of interest (Section 8.5.6.2) to complete the questionnaire at early discontinuation or study exit and monthly for 6 months.

GI, gastrointestinal; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0.