Aimmune Therapeutics, Inc.

CLINICAL STUDY PROTOCOL

Protocol Title:	Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON)
Protocol Identifier:	ARC005
Phase:	3
Investigational Product:	AR101, also known as Palforzia, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp in the United States, and defatted powder of *Arachis hypogaea* L., semen (peanuts) in the European Union
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Blvd, Suite 300 Brisbane, CA 94005 United States
Reference Numbers:	IND 15463, NCT03736447, EudraCT 2018-001749-15
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Original Protocol:	0.0 – 31 May 2018
Global Amendments	**Country/Region-Specific Amendments**
1.0 – 27 Jun 2019	Country (France): 0.1 – 10 May 2019
2.0 – 02 Mar 2020	Country (Germany): 0.2 – 31 May 2019
3.0 – 29 May 2020	Country (France, United Kingdom): 1.1 – 19 Sep 2019
4.0 – 17 Mar 2021	

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

SYNOPSIS

Title of Study: Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON)

Short Title: POSEIDON

Protocol Identifier: ARC005

Reference Numbers: IND 15463, NCT03736447, EudraCT 2018-001749-15

Phase of Development: 3

Number of Subjects: Approximately 132

Study Centers: Approximately 25 in North America and Europe

Purpose of the Study: To determine the efficacy and safety of AR101 compared with placebo in peanut-allergic children aged 1 to < 4 years.

Study Objectives:

Primary:

- Efficacy of AR101 treatment in peanut-allergic subjects aged 1 to < 4 years, assessed by tolerability of specified single doses of peanut protein in a double-blind, placebo-controlled food challenge (DBPCFC)

Secondary:

- Safety and tolerability of study treatment
- Efficacy of AR101, assessed by tolerability of other specified single doses of peanut protein in a DBPCFC
- Maximum severity of allergy symptoms in a DBPCFC

Exploratory:

- Immunologic changes
- Changes in control of pre-existing atopic disease (asthma, atopic dermatitis)

Study Design:

This is a phase 3, international, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic children aged 1 to < 4 years. The study will be conducted at approximately 25 study sites in North America and Europe.

Eligible subjects who develop age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC will be randomly assigned 2:1 to blinded treatment with AR101 or placebo. Randomization will be stratified by geographic region (North America, Europe).

Subjects will begin initial dose escalation under medical supervision at the study site on day 1 with a stepwise dose escalation of study product (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate the 3 mg dose on day 1 will return on day 2 for a single 1 mg dose. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin the up-dosing period. Subjects who do not tolerate any dose on day 1 or day 2 will discontinue early from the study.

The up-dosing period will be approximately 6 months (maximum 40 weeks), with dose escalation approximately every 2 weeks. Daily doses of study product during up-dosing will be 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of study product at each new dose level will be administered under medical supervision at the study site; the remaining doses at each dose level will be administered daily at home as tolerated. Dose adjustments may be allowed. Subjects who tolerate the 300 mg/day dose for 2 weeks within 40 weeks will begin the maintenance period. Subjects unable to tolerate the 300 mg/day dose for 2 weeks within 40 weeks of up-dosing will discontinue early from the study.

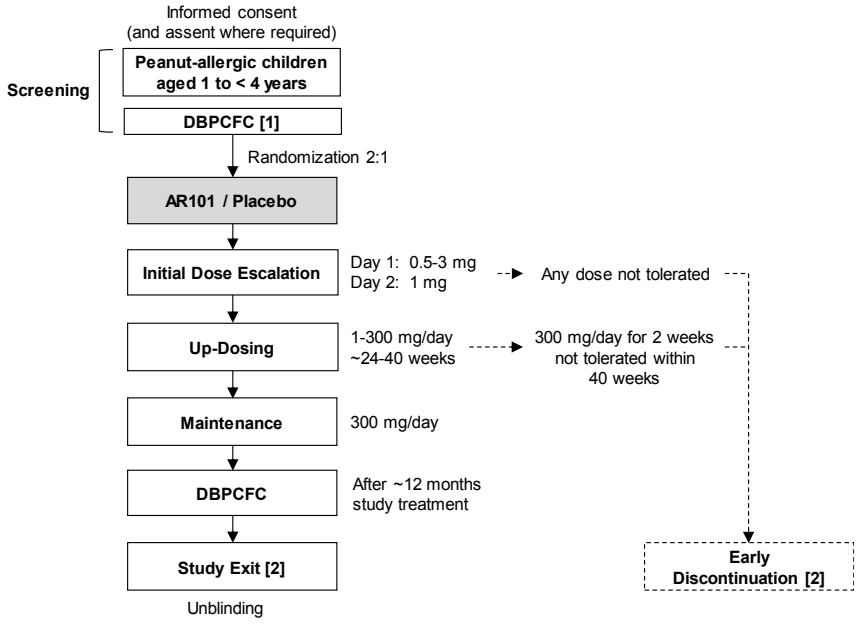
Subjects who begin maintenance treatment will continue daily dosing with study product at 300 mg/day for an overall total of approximately 12 months of treatment, with study site visits every 4 weeks. The duration

of maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks). Dose adjustments may be allowed. After the end of maintenance, subjects will have an exit DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative). The 300 mg daily dose of study product must be tolerated for at least 2 consecutive weeks before having the DBPCFC. Subjects who complete both days of the exit DBPCFC will exit (complete) the study. Study treatment assignment will be unblinded for a subject after all major data queries for the subject are resolved. Eligible subjects will have the option to enroll in an open-label, follow-on study to receive AR101 treatment. If the follow-on study is not yet available at the study site, blinded study treatment may continue and the visit schedule will be every 4 weeks until the follow-on study is available.

At early discontinuation or study exit, subjects with unresolved adverse events or who had gastrointestinal (GI) adverse events of interest (ie, GI adverse events that result in dose interruption > 7 consecutive days or early discontinuation) will have safety follow-up.

An independent, external data and safety monitoring committee (DSMC) will monitor safety on a periodic basis.

Study Schematic:



[1] Eligible subjects must have age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in the screening DBPCFC.

[2] Subjects with unresolved adverse events or who had gastrointestinal adverse events of interest will have safety follow-up.

DBPCFC, double-blind, placebo-controlled food challenge.

Key Eligibility Criteria:

Subjects must be aged 1 to < 4 years at randomization, have written informed consent from a parent/guardian, provide assent (where required and as appropriate per local requirements), and have sensitivity to peanut, defined as one of the following: no known history of peanut ingestion and serum IgE to peanut of ≥ 5 kUA/L within 12 months before randomization, or a documented history of peanut allergy and a mean wheal diameter on skin prick test (SPT) to peanut of at least 3 mm greater than the negative control (diluent) or serum immunoglobulin E (IgE) to peanut of ≥ 0.35 kUA/L, obtained within 12 months before randomization. Subjects must have age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC. A palatable vehicle food to which the subject is not allergic must be available for administering study product. Subjects must not have a history of severe or life-threatening anaphylaxis; history of hemodynamically significant cardiovascular or renovascular disease (including uncontrolled or inadequately controlled hypertension); history of

biopsy-confirmed diagnosis of eosinophilic esophagitis (EoE); other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); symptoms of dysphagia; recurrent GI symptoms considered clinically significant in the opinion of the investigator; history of a mast cell disorder; have moderate or severe persistent asthma, or mild asthma that is uncontrolled or difficult to control; history of high-dose corticosteroid medication use; history of food protein-induced enterocolitis syndrome (FPIES) within 12 months before screening; recurrent urticaria; history of failure to thrive or any other form of abnormal growth, or developmental or speech delay that precludes age-appropriate communication; or any other condition 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.

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 peanut protein. AR101 will also be provided as 300 mg peanut protein in foil-laminate sachets. 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 parent/caregiver as appropriate for the assigned dose level.

Reference Therapy, Dose, and Mode of Administration:

Placebo is formulated with the same inactive ingredients as AR101 and without peanut flour. Placebo containing excipients that are color-matched with the peanut flour will be provided as matching capsules identical to the AR101 capsules. Matching placebo-containing sachets are also provided. Capsules/sachets will be opened; the contents delivered over an age-appropriate, semisolid vehicle food; and mixed thoroughly.

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

Duration of Treatment:

The total duration of treatment is approximately 12 months (eg, 48-54 weeks) for each subject.

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

Statistical Methods:

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

All efficacy analyses will be conducted using the intent-to-treat (ITT) population, defined as all subjects randomly assigned to study treatment who receive any part of 1 dose of study product. Randomization will be central and treatment allocation will be 2:1 (AR101 or placebo). Randomization will be stratified by geographic region (North America, Europe); at least 30% of subjects are planned to be enrolled in Europe.

The primary and secondary efficacy endpoints are defined by major health authority region (North America and Europe):

Primary Efficacy Endpoint:

- North America: The primary efficacy endpoint is the proportion of subjects treated with AR101 compared with placebo who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
  - The Farrington-Manning test will be used to test the null hypothesis that the difference in desensitization response rate (AR101-placebo) is equal to 0.15 at the two-sided 0.05 significance level. Desensitization response rates and associated 95% CIs will be presented for each treatment group using exact Clopper-Pearson CIs.
- Europe: The primary efficacy endpoint is the proportion of subjects treated with AR101 compared with placebo who tolerate an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
  - The Farrington-Manning test will be used to test the null hypothesis that the difference in desensitization response rate is 0 at the two-sided 0.05 significance level. Desensitization response

rates and associated 95% CIs will be presented for each treatment group using exact Clopper-Pearson CIs.

Secondary Efficacy Endpoints: The following secondary efficacy endpoints will be evaluated in hierarchical order by region (North America and Europe) if the primary efficacy endpoint analysis is significant at the 0.05 level.

North America

1. Proportion of subjects who tolerate an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
2. Proportion of subjects who tolerate an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC.

Europe

1. Proportion of subjects who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
2. Proportion of subjects who tolerate an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC.

Safety Endpoints:

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

Safety data will be collected from signed informed consent and assent (where required) through 14 days after the last dose of study product, or through study exit for subjects receiving AR101 treatment in a follow-on study. Safety follow-up data will be collected for at least 30 days after early discontinuation or study exit for subjects with unresolved adverse events, or for 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, modified 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. Adverse events of interest include anaphylaxis, GI adverse events with prolonged dose interruption (> 7 consecutive days) or that result in early discontinuation, accidental and nonaccidental food allergen exposure, severe adverse events, and use of epinephrine.

The safety of AR101 treatment versus placebo 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, 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 Test for Respiratory and Asthma Control in Kids (TRACK), Eczema Area and Severity Index (EASI), and laboratory data if relevant.

Exploratory Endpoints:

Exploratory endpoints will be assessed as follows:

- Change from baseline in peanut-specific and peanut component-specific serum immunoglobulins.
- Change from baseline in mean wheal diameter and mean erythema diameter on SPT to peanut.
- Change from baseline in TRACK and EASI scores.
- Palatability of study treatment, assessed using a palatability survey.
- Proportion of subjects who tolerate a single highest dose of 2000 mg peanut protein (4043 mg cumulative) during the exit DBPCFC.

- Change from baseline in the single highest tolerated dose of peanut protein at the exit DBPCFC.
- Maximum dose of peanut protein reached with no more than mild allergy symptoms at the exit DBPCFC.

Sample Size Considerations:

A sample size of 132 subjects randomly assigned at a ratio of 2:1 to AR101 (88 subjects) or placebo (44 subjects) provides sufficient power to detect a treatment difference for the primary efficacy analysis for each major health authority region (North America and Europe) as follows:

- For North America, the sample size provides 85% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo with an at least 15% margin for the primary efficacy endpoint of the proportion of subjects tolerating an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on the Farrington and Manning method for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the DBPCFC of 55% in AR101-treated subjects, and a maximum desensitization rate of 15% in placebo-treated subjects, conducted in the ITT population.
- For Europe, the sample size provides > 95% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo for the primary efficacy endpoint of the proportion of subjects tolerating an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on the Farrington and Manning method for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the DBPCFC of 50% in AR101-treated subjects, and a maximum desensitization rate of 10% in placebo-treated subjects, conducted in the ITT population.

The desensitization rates used in the sample size calculations account for an estimated 25% of subjects across both treatment groups to drop out or discontinue early from the study; these subjects will not be replaced and will be considered nonresponders.

Guidance on Study Conduct During a Pandemic, Epidemic, or Other Emergency Not Related to the Study:

In the event of a pandemic (eg, Coronavirus Disease 2019 [COVID-19] pandemic), epidemic, or other emergency not related to the study (eg, natural disaster, act of war or terrorism), restrictions may be issued at the country, state, regional, and/or local level that may affect study conduct, the scientific integrity of the study, or the safety and well-being of study participants and study site staff. When such restrictions and associated challenges (eg, site closures; travel restrictions; quarantines; pandemic- or epidemic-related illness in subjects, parents, caregivers, or study site personnel) prevent the conduct of study site visits (ie, onsite) or access to study product for an extended period, changes to certain study procedures will be implemented in accordance with regulatory requirements to ensure subject safety and continued treatment, care, and sponsor oversight as described in Appendix 3 of the protocol.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
CFR	Code of Federal Regulations
CoFAR	Consortium of Food Allergy Research
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind, placebo-controlled food challenge
DSMC	Data and safety monitoring committee
EAACI	European Academy of Allergy and Clinical Immunology
EASI	Eczema Area and Severity Index
EC	Ethics committee (global term including institutional review boards, independent ethics committees, research ethics committees, and the like)
EoE	Eosinophilic esophagitis
EU	European Union
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
ICH	International Council for Harmonisation
ID	Identification
Ig	Immunoglobulin
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OIT	Oral immunotherapy
PEESS v2.0	Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0
SPT	Skin prick test
TRACK	Test for Respiratory and Asthma Control in Kids
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

Aimmune Therapeutics, Inc., a Nestlé Health Science Company (Aimmune) developed AR101, also known as Palforzia, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp in the United States, and defatted powder of *Arachis hypogaea* L., semen (peanuts) in the European Union (EU), using a characterized oral immunotherapy (OIT) desensitization approach for patients with peanut allergy.

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 milligrams (or less) 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 for patients with peanut allergy and their families (Anagnostou, 2014; Avery, 2003; Primeau, 2000).

Early clinical studies of peanut 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 for subjects with peanut allergy.

More recently, results of a small, randomized, double-blind, single-center study of early intervention peanut OIT in peanut-allergic children aged 9 to 36 months (the DEVIL study) suggest that OIT is safe, efficacious, and feasible in this age group (Vickery, 2017). A total of 37 patients were randomly assigned 1:1 to receive peanut OIT at target maintenance doses of 300 mg/day or 3000 mg/day. Most patients had atopic disease: 27% had asthma or recurrent wheeze, 70% had atopic dermatitis, and 22% had allergic rhinitis. The 300 mg/day maintenance dose of peanut protein was sufficient to induce a high rate of immune modulation and beneficial clinical outcomes after a median of 29 months of treatment; 17 of 20 patients (85%) who received 300 mg/day maintenance treatment tolerated 5 g peanut protein cumulative without dose-limiting allergy symptoms in a double-blind, placebo-controlled food challenge (DBPCFC). The overall safety profile was favorable and similar to that in other peanut OIT studies. Most treatment-related allergy symptoms were mild and occurred more frequently during the build-up phase, compared with the maintenance phase. Recently, the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology workgroup published guidance for conducting an oral food challenge to peanut in an infant based on available evidence and expert consensus (Bird, 2017). Taken together, these studies support further clinical development of AR101 in peanut-allergic subjects aged 1 to < 4 years.

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 peanut protein with no more than mild allergy symptoms. This state of desensitization is hypothesized to be sufficient to reduce the incidence and severity of allergic reactions, including anaphylaxis, in a peanut-allergic patient after accidental exposure to peanut. 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 peanut protein elicited an allergic reaction in 1% of peanut-allergic patients and 2.1 mg peanut protein elicited an allergic reaction in 5% of peanut-allergic patients. In one 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 peanut protein (range, 34-177 mg). The eliciting dose was < 5 mg 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 peanut protein is expected to be clinically meaningful for 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).

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 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 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 2 weeks of maintenance treatment at 300 mg/day, subjects had an exit DBPCFC with up to 600 mg peanut protein (1043 mg cumulative) or placebo (oat flour). All 23 AR101-treated subjects tolerated a single challenge dose of at least 300 mg peanut protein (443 mg cumulative) 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 a single challenge dose of 600 mg peanut protein (1043 mg cumulative) 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 a single challenge dose of 300 mg peanut protein (443 mg cumulative). 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 a single dose of at least 300 mg peanut protein with no more than mild allergy 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 peanut protein, the equivalent of approximately 1 to 2 whole peanut kernels (Baumert, 2018), is clinically

relevant and expected to reduce the incidence and severity of allergic reactions, including anaphylaxis, in a peanut-allergic patient after accidental exposure to peanut.

1.2.2 Phase 3 Pivotal Studies ARC003, ARC010, and ARC007

ARC003 was an international, randomized, double-blind, placebo-controlled phase 3 study of the efficacy and safety of AR101 in peanut-allergic children and adults aged 4 to 55 years (PALISADE group of clinical investigators, 2018). The study consisted of a screening phase (including a DBPCFC), a double-blind OIT treatment phase (including initial dose escalation [2 days], up-dosing [20-40 weeks], and maintenance [approximately 6 months]), and an exit DBPCFC. Of 555 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 dose of at least 600 mg 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% (95% CI: 53.0, 73.3; $p < 0.0001$). In addition, 50.3% of AR101-treated subjects tolerated a single dose of 1000 mg peanut protein (2043 mg cumulative), compared with 2.4% of placebo-treated subjects (95% CI: 38.0, 57.7; $p < 0.0001$). Of subjects aged 4 to 17 years, 296 AR101-treated subjects and 116 placebo-treated subjects had an evaluable exit DBPCFC (ie, completed at least the peanut food challenge day; completer population). A single 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).

AR101 was generally well tolerated in the safety population of subjects aged 4 to 17 years (372 AR101, 124 placebo). The safety profile remains consistent with previous findings of hypersensitivity events (allergic reactions), manifesting primarily as mild to moderate gastrointestinal (GI) symptoms in decreasing order of abdominal pain, vomiting, pruritus, upper abdominal pain, cough, throat irritation, oral pruritus, nausea, urticaria, and rhinorrhea that generally decreased in incidence with treatment from up-dosing to maintenance. When adjusted for exposure, the most frequent adverse events and symptoms overall in the AR101 group were throat irritation, oral pruritus abdominal pain, upper abdominal pain, nausea, and oral paresthesia. One event of biopsy-confirmed eosinophilic esophagitis (EoE) was reported. No subject died or had any life-threatening adverse event or symptom, and the incidence of treatment-related severe events for AR101-treated subjects was low (2.4%). The incidence of serious adverse events for AR101-treated subjects was also low (2.2%), including 3 with anaphylactic reaction (1 severe [anaphylaxis] in a subject with high peanut-specific immunoglobulin [Ig] E > 100 kUA/L at baseline) and 2 with exacerbation of asthma. All serious adverse events resolved. Systemic allergic reactions (Medical Dictionary for Regulatory Activities [MedDRA] preferred term anaphylactic reaction) were generally mild or moderate severity and resolved rapidly with treatment; 1 event was serious and severe anaphylaxis as just described. Epinephrine was used by 14.0% of AR101-treated subjects and 6.5% of placebo-treated subjects, and the majority of use was for mild or moderate adverse events and symptoms (including systemic allergic reactions) after study

product dosing at home during up-dosing and maintenance. About 10% of subjects discontinued due to adverse events, and most discontinuations were due to GI events during up-dosing. Adverse events associated with accidental food allergen exposure were less common overall in the AR101 group, possibly indicating less vulnerability to peanut exposure over time with treatment. 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).

ARC010 was a randomized, double-blind, placebo-controlled phase 3 study of the efficacy and safety of AR101 in peanut-allergic subjects aged 4 to 17 years conducted in Europe. The dosing regimen used was the same as for study ARC003, except that the maintenance period was approximately 3 months. The primary and all key secondary efficacy endpoints were met. In the ITT population of subjects aged 4 to 17 years (132 AR101, 43 placebo), 58.3% of AR101-treated subjects and 2.3% of placebo-treated subjects tolerated a single dose of 1000 mg peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC (treatment difference, 56.0%; 95% CI: 44.1, 65.2; $p < 0.0001$). A total of 68.2% of AR101-treated subjects and 9.3% of placebo-treated subjects tolerated a single dose of 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC (treatment difference, 58.9%; 95% CI: 44.2, 69.3; $p < 0.0001$). AR101 was generally well tolerated and the overall safety profile appeared acceptable, and the results were consistent with the results of study ARC003.

ARC007 was a randomized, double-blind, placebo-controlled, real-world safety study of AR101 in peanut-allergic subjects aged 4 to 17 years conducted in North America. The study consisted of screening, initial dose escalation (2 days), up-dosing (20-42 weeks), and at least 2 weeks of maintenance at 300 mg/day. A total of 506 subjects aged 4 to 17 years were randomly assigned to study treatment (338 in the AR101 group and 168 in the placebo group). The overall safety profile of AR101 appeared acceptable and was consistent with previous studies of AR101 in peanut-allergic subjects aged 4 to 17 years; no new safety concerns were identified in this study.

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.

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.

The AR101 development program has focused on sensitive peanut-allergic individuals. In the pivotal phase 3 study ARC003, no subject in the pediatric group aged 4 to 17 years

(N = 496) tolerated a single dose of peanut protein greater than 30 mg in the screening DBPCFC. At the exit DBPCFC, approximately 77% AR101-treated subjects compared with approximately 8% placebo-treated subjects had a single highest tolerated dose of 300 to 1000 mg peanut protein. In the phase 2 study ARC001, no subject was able to consume more than a single highest dose of 30 mg peanut protein (43 mg cumulative) 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 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 GI hypersensitivity events (Section 1.2.2), consistent with the low-grade and repeated stimulation of the immune system required to produce desensitization during allergen immunotherapy.

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 the study is to determine the efficacy and safety of AR101 compared with placebo in peanut-allergic children aged 1 to < 4 years.

1.6 Rationale for Study Design

The majority of peanut allergy cases develop in infancy or early childhood and tend to persist into adulthood; about 20% of those affected outgrow their allergy (Nwaru, 2014; Husain, 2012; Sicherer, 2010a). Currently, no pharmaceutical product is approved for desensitizing persons with peanut allergy with the therapeutic intent of minimizing the risk of a severe allergic reaction in case of accidental exposure to peanut. Therefore, a significant unmet medical need remains for an effective treatment for peanut allergy in people of all ages.

Although allergic reactions can be dangerous in people of any age, young children are particularly vulnerable because they may not be able to understand or communicate what or how they are feeling when experiencing an allergic reaction. Adults may have difficulty recognizing anaphylaxis in young children because many of the early signs and symptoms mirror those of healthy infants and toddlers. These include manifestations of the GI system (drooling, regurgitating, vomiting, diarrhea, dysphagia), behavior (crying, irritability,

clinging to a caregiver, scratching, loss of bowel or bladder continence), respiratory system (dysphonia), skin (flushing), and mental status (drowsiness, somnolence) (Simons, 2015; Dosanjh, 2013). Severe allergic reactions involving multiple organ systems necessitate immediate use of rescue medication such as epinephrine.

Initiation of peanut allergen exposure using OIT in early life may have unique benefits for children at high risk to develop allergy to peanut. Recent studies of allergen priming in young children suggest that allergen-specific IgE responses are common early in life and may emerge before committed Th2 differentiation (Asarnoj, 2017; Neuman-Sunshine, 2012; Sicherer, 2010b; Ho, 2008). However, the presence of weak T-cell receptor affinity and uncommitted Th2 differentiation in infants and young children suggest that developmental plasticity may exist in early allergic responses, even in infants at high risk for peanut allergy who were already producing peanut-specific IgE (Sicherer, 2010b; Rowe, 2007).

In the landmark LEAP trial (Learning Early About Peanut Allergy), early oral exposure to peanut in infants with high-risk atopic disease was immunomodulatory and prevented peanut allergy, including in infants already sensitized but not yet allergic to peanut (Du Toit, 2016; Du Toit, 2015). Although previous studies demonstrated the safety and efficacy of OIT in desensitizing peanut-allergic children and adolescents, the outcomes of OIT in children aged < 4 years are not well characterized. The results of a small, randomized, double-blind, single-center study of low-dose and high-dose peanut early intervention OIT (the DEVIL study) demonstrated that OIT dosing and DBPCFCs are feasible and can be performed safely in children aged 9 to 36 months (Vickery, 2017). Additionally, a 300 mg/day maintenance dose of peanut protein was sufficient to induce a high rate of immune modulation and beneficial clinical outcomes after a median of 29 months of treatment. The treatment benefits of early intervention OIT may be due to the lower average peanut-specific IgE levels more commonly observed in young children. An inverse association between OIT outcomes and baseline peanut-specific IgE was demonstrated previously (Vickery, 2014).

Based on these observations, study ARC005 is designed to assess the efficacy and safety of AR101 in peanut-allergic children aged 1 to < 4 years. The primary objective of the study is to determine the efficacy of AR101 through increasing threshold reactivity in DBPCFCs.

2 STUDY OBJECTIVES

2.1 Primary Objective

- Efficacy of AR101 treatment in peanut-allergic subjects aged 1 to < 4 years, assessed by tolerability of specified doses of peanut protein in a DBPCFC

2.2 Secondary Objectives

- Safety and tolerability of study treatment
- Efficacy of AR101, assessed by tolerability of other specified single doses of peanut protein in a DBPCFC
- Maximum severity of allergy symptoms in a DBPCFC

2.3 Exploratory Objectives

- Immunologic changes
- Changes in control of pre-existing atopic disease (asthma, atopic dermatitis)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This is a phase 3, international, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic children aged 1 to < 4 years. The study will be conducted at approximately 25 study sites in North America and Europe.

Eligible subjects who develop age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC will be randomly assigned 2:1 to blinded treatment with AR101 or placebo. Randomization will be stratified by geographic region (North America, Europe).

Subjects will begin initial dose escalation under medical supervision at the study site on day 1 with a stepwise dose escalation of study product (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate the 3 mg dose on day 1 will return on day 2 for a single 1 mg dose. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin the up-dosing period. Subjects who do not tolerate any dose on day 1 or day 2 will discontinue early from the study.

The up-dosing period will be approximately 6 months (maximum 40 weeks), with dose escalation approximately every 2 weeks. Daily doses of study product during up-dosing will be 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of study product at each new dose level will be administered under medical supervision at the study site; the remaining doses at each dose level will be administered daily at home as tolerated. Dose adjustments may be allowed. Subjects who tolerate the 300 mg/day dose for 2 weeks within 40 weeks will begin the maintenance period. Subjects unable to tolerate the 300 mg/day dose for 2 weeks within 40 weeks of up-dosing will discontinue early from the study.

Subjects who begin maintenance treatment will continue daily dosing with study product at 300 mg/day for an overall total of approximately 12 months of treatment, with study site visits every 4 weeks. The duration of maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks). Dose adjustments may be allowed. After the end of maintenance, subjects will have an exit DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative). The 300 mg daily dose of study product must be tolerated for at least 2 consecutive weeks before having the DBPCFC. Subjects who complete both days of the exit DBPCFC will exit (complete) the study. Study treatment assignment will be unblinded for a subject after all major data queries for the subject are resolved. Eligible subjects will have the option to enroll in an open-label, follow-on study to receive AR101 treatment. If

the follow-on study is not yet available at the study site, blinded study treatment may continue and the visit schedule will be every 4 weeks until the follow-on study is available.

At early discontinuation or study exit, subjects with unresolved adverse events or who had GI adverse events of interest (ie, GI adverse events that result in dose interruption > 7 consecutive days or early discontinuation) will have safety follow-up.

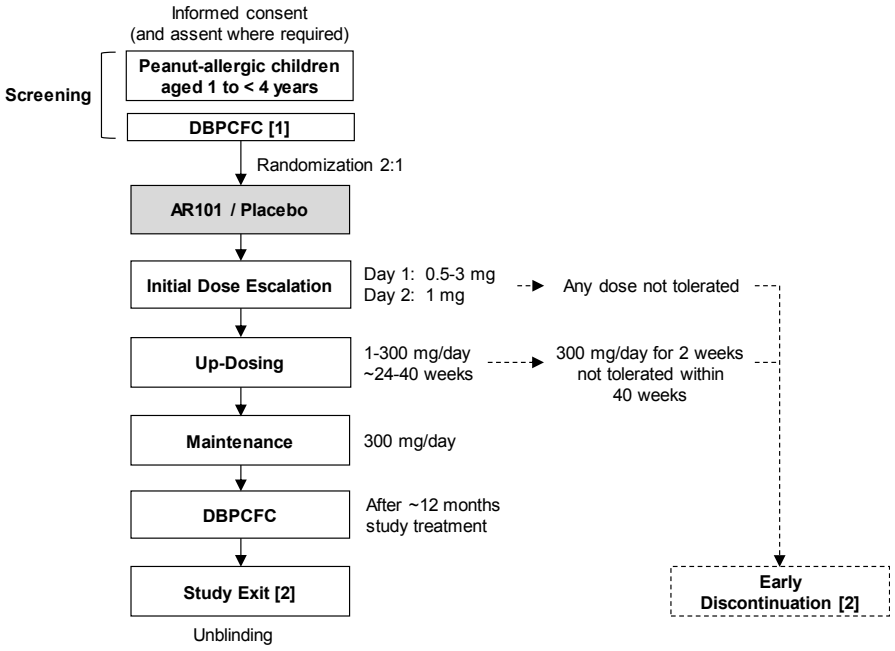
An independent, external data and safety monitoring committee (DSMC) will monitor safety on a periodic basis.

In the event of a pandemic (eg, Coronavirus Disease 2019 [COVID-19] pandemic), epidemic, or other emergency not related to the study (eg, natural disaster, act of war or terrorism), restrictions may be issued at the country, state, regional, and/or local level that may affect study conduct, the scientific integrity of the study, or the safety and well-being of study participants and study site staff. When such restrictions and associated challenges (eg, site closures; travel restrictions; quarantines; pandemic- or epidemic related illness in subjects, parents, caregivers, or study site personnel) prevent the conduct of study site visits (ie, onsite) or access to study product for an extended period, changes to certain study procedures will be implemented in accordance with regulatory requirements to ensure subject safety and continued treatment, care, and sponsor oversight as described in Appendix 3.

3.2 Study Schematic

The study schematic is provided in Figure 1.

Figure 1: Study Schematic



[1] Eligible subjects must have age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in the screening DBPCFC.

[2] Subjects with unresolved adverse events or who had gastrointestinal adverse events of interest will have safety follow-up.

DBPCFC, double-blind, placebo-controlled food challenge.

3.3 Blinding

Study treatments and immunology laboratory results obtained after screening will be blinded. All subjects, study site personnel (including investigators), and sponsor staff and its representatives will be blinded to treatment identity, except the designated unblinded person who will access the interactive response system to obtain the randomization order for the peanut protein and placebo challenge days, and prepare the DBPCFC material.

Study treatment assignment will be unblinded for each subject after completion of their exit DBPCFC and after all major data queries for the subject are resolved.

3.4 Study Suspension Criteria

The study will be suspended if any of the following occur:

- A treatment-associated death in a subject receiving AR101 in this study
- Two subjects hospitalized within 6 months of each other for intensive treatment due to AR101-related adverse events

- Three subjects hospitalized for intensive treatment due to AR101-related adverse events
- Greater than 2 cases of AR101-related anaphylaxis resulting in hypotension, neurologic compromise, or mechanical ventilation (modified European Academy of Allergy and Clinical Immunology [EAACI] grade 3 per Section 8.5; clinical assessment per Section 8.6.1.1)

Admission to the hospital for observation only (not for intensive treatment of a serious AR101-related adverse event) will not be considered contributory to the study suspension criteria. The DSMC may also recommend halting the study for any substantial imbalance in adverse events apart from anticipated study product-related allergy symptoms, based on review of the safety data.

In the event of study suspension based on the above criteria, enrollment and dose escalation will be halted. Dosing at the current tolerated dose level will continue unless otherwise directed by the sponsor or by the regulatory authority for a participating country. Study suspension will not be lifted until after the safety data are discussed with regulatory authorities and the regulatory authorities agree with resuming enrollment and dose escalation.

The sponsor may suspend the study in the event of a pandemic, epidemic, or other emergency not related to the study if the resulting restrictions do not permit conduct of the alternate procedures described in Appendix 3. Study suspension will not be lifted until after consideration of individual subjects; study sites; and local, state, regional, and national guidance as applicable; and in accordance with regulatory requirements.

3.5 Duration of Study

The total duration of treatment is approximately 12 months (eg, 48-54 weeks) for each subject.

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

The total duration of the study and duration of study treatment for individual subjects may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Section 2.3 of Appendix 3.

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 1 to < 4 years at randomization.
2. Written informed consent from the legal guardian/parent (or both parents where required by local authorities). Provide assent where required and as appropriate per local requirements.
3. Sensitivity to peanut, defined as one of the following:
   a. No known history of peanut ingestion and has serum IgE to peanut ≥ 5 kUA/L within 12 months before randomization.
   b. Documented history of physician-diagnosed IgE-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, and has a mean wheal diameter on skin prick test (SPT) to peanut of at least 3 mm greater than the negative control (diluent) or serum IgE to peanut ≥ 0.35 kUA/L, obtained within 12 months before randomization.

   *Characteristic signs and symptoms of IgE-mediated allergic reactions are generally objective and affect the target organs of skin, 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

4. Development of age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC.
5. A palatable vehicle food to which the subject is not allergic must be available for administering study product.

4.2 Exclusion Criteria

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

1. History of severe or life-threatening anaphylaxis anytime before the screening DBPCFC.
2. History of hemodynamically significant cardiovascular or renovascular disease, including uncontrolled or inadequately controlled hypertension.

3. History of biopsy-confirmed diagnosis of EoE; other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); or symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck").
4. Recurrent GI symptoms considered clinically significant in the opinion of the investigator.
5. History of a mast cell disorder including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema.
6. Moderate or severe persistent asthma (criteria steps 3-6; National Heart, Lung, and Blood Institute [NHLBI], 2007).
7. Mild asthma (criteria steps 1-2; NHLBI, 2007) that is uncontrolled or difficult to control based on NHLBI 2007 criteria.
8. History of high-dose corticosteroid use (eg, 1-2 mg/kg prednisone or equivalent for > 3 days) by any route of administration as defined by any of the following:
   - Steroid administered daily for > 1 month within 1 year before screening
   - One steroid course within 6 months before screening
   - More than 2 steroid courses ≥ 1 week in duration within 1 year before screening
9. History of food protein-induced enterocolitis syndrome (FPIES) within 12 months before screening.
10. Recurrent urticaria.
11. History of failure to thrive or any other form of abnormal growth, or developmental or speech delay that precludes age-appropriate communication.
12. History of chronic disease (except mild intermittent asthma, mild persistent asthma that is controlled, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in a chronic therapeutic regimen.
13. Unable to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction for 5 half-lives of the medication before the screening SPT, first day of dose escalation, and DBPCFCs.
14. Use or anticipated use of a prohibited medication (eg, beta blockers [oral], angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or tricyclic antidepressants), monoclonal antibody, or any other immunomodulatory therapy (including immunosuppressive medications).
15. Treatment with any form of immunotherapy for any food allergy anytime before screening.
16. Participation in another clinical trial within 30 days or 5 half-lives of the investigational product, whichever is longer, before screening.
17. Allergy to oat or rice.
18. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector.
19. Parent/caregiver unable or unwilling to use epinephrine auto-injectors.
20. Unable to follow the protocol requirements.
21. 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.

22. Resides at the same place as another subject in any AR101 interventional trial.
23. Lives in the same household and/or is a family member of a sponsor employee or site staff involved in conducting this study.

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 study product will include initial dose escalation, up-dosing, and maintenance.

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).

Enrollment and study procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

5.1 Screening Period

The 42-day screening period will be from day -42 through day -1. The screening period will commence after signed informed consent and assent (where required) are 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 parents/guardians of potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent and assent (where required) 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 and assent (where required), 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 with written informed consent and assent (where required) who subsequently do not meet eligibility criteria or if consent is withdrawn, 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 Appendix 4. All screening procedures must be completed within 42 days after signed informed consent and assent (where required) are obtained. Screening procedures should be completed early in the window to avoid potential delays due to scheduling issues or intercurrent illness.

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. Signed informed consent and assent (where required) must be reobtained before any rescreening procedures are conducted unless the procedures are part of routine standard of care. Screening laboratory and SPT procedures completed at the time of initial screening do not need to be repeated if rescreening occurs within 6 months.

5.2 Treatment Periods

5.2.1 Treatment Period Visit Windows

The combined windows for screening procedures (from signed informed consent/assent to randomization) and start of randomized study treatment must not exceed 42 days. All up-dosing and maintenance study site visits have a visit window of ±3 days (ie, 3 days before or after the expected visit day). The initial dose-escalation day 1 visit must be within 10 days after the screening DBPCFC. 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.

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, study site personnel will access the interactive response system to assign subjects to randomized study treatment (AR101 or placebo). Randomized study treatment is to begin within 42 days after signed consent/assent and should be the same day as randomization, or within 3 days (inclusive) after randomization if starting the same

day is not feasible (eg, for circumstances such as intercurrent illness or visit scheduling issues).

5.2.3 General Study Visit Procedures

Day 1 will be the first day of randomized study treatment (AR101 or placebo). Study procedures will be performed at each visit according to the schedule of activities (Appendix 5).

Before administration of the first and any subsequent dose of study product 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. Signs and symptoms of an allergic reaction will be evaluated, and monitoring will continue through the end of the observation period as follows:

- Symptoms of allergic reactions will be evaluated per Section 8.6.1.
- The tolerability of study product will be evaluated per Section 8.6.1.2.
- The treatment of allergic reactions and dose adjustment of study product will follow guidelines per Section 8.6.2 and Section 8.6.3.

On the day after each study site visit, site staff will contact the parent/caregiver by telephone to perform the following (Appendix 5):

- Inquire if any adverse events occurred (including allergy symptoms, GI symptoms, and exposure to food allergen).
- Provide guidance in managing adverse events.
- Remind the parent/caregiver to record the subject's symptoms in the study diary.
- Inquire about compliance with study product dosing.

5.2.3.1 Initial Dose-Escalation Procedures

Initial dose-escalation procedures are listed in Appendix 5. Subjects may have clear liquids or flavored gelatin during the dosing procedures.

Day 1

Subjects will be required to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction for 5 half-lives of the medication before the first day of dose escalation.

Study product will be administered in 4 increasing doses in a stepwise manner in 20- to 30-minute intervals as tolerated. The 4 doses and cumulative dose of study product to be consumed on day 1 are shown in Table 1.

Table 1: Study Product Single Doses and Cumulative Dose on Day 1

Dose Number	Study Product Dose (mg)	Cumulative Dose (mg)
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6

The time points for study product dosing and assessments of vital signs and allergic reaction are provided in Table 2. Subjects who develop dose-limiting, moderate, or severe allergy symptoms at any dose of study product, or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.6.3.1) will stop dose escalation and discontinue early from the study (Section 5.3).

Table 2: Initial Dose-Escalation Day 1 Procedures

Study Product Dose (Timing) Time Point	Administer Study Product	Vital Signs [1]	Assess Allergy Symptoms
Predose		X	
0.5 mg	X		
15-30 min postdose		X	X
1 mg (20-30 min after previous dose) [2]	X		
15-30 min postdose		X	X
1.5 mg (20-30 min after previous dose) [2]	X		
15-30 min postdose		X	X
3 mg (20-30 min after previous dose) [2]	X		
15-30 min postdose		X	X
Approximately every 30 min until at least 90 min after last dose or end of observation per allergy symptoms [3]		X	X

[1] Vital signs include blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation level.

[2] If the previous dose was tolerated (Section 8.6.1.2). If the subject has dose-limiting, moderate, or severe symptoms at any dose, or requires rescue medications (except ≤ 2 doses of antihistamines, Section 8.6.3.1), stop dose escalation and discontinue the subject early from the study. If 3 mg is tolerated, the subject will return for a single 1 mg dose on day 2.

[3] The length of observation is based on signs/symptoms of allergic reaction per Section 8.6.1.

Min, minutes.

Day 2

Subjects who tolerate 3 mg study product on day 1 will return to the study site on day 2 to receive a single 1 mg dose under medical supervision. Day 2 should be the next consecutive day after day 1. If circumstances create a safety risk (eg, an intercurrent illness), day 2 may be delayed up to 7 days after day 1. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will receive an adequate supply of study product to continue daily dosing at home at 1 mg/day during up-dosing (Section 5.2.3.2).

Subjects who are unable to return to the study site ≤ 7 days after day 1 for day 2 procedures or who develop dose-limiting, moderate, or severe symptoms after consuming the 1 mg dose on day 2, or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.6.3.1), will stop study product dosing and discontinue early from the study (Section 5.3).

5.2.3.2 Up-Dosing Procedures

Up-dosing procedures are listed in the schedule of activities in Appendix 5.

Up-dosing study site visits are every 2 weeks for approximately 6 months (minimum 24 weeks if up-dosing proceeds without holding or reducing a dose level; maximum 40 weeks).

Up-dosing will begin when subjects begin daily dosing with study product at 1 mg/day at home for 2 weeks. Subjects who tolerate 1 mg/day for 2 weeks will return to the study site to receive a 3 mg dose. Subjects who tolerate the 3 mg dose at the study site will receive study product to continue daily dosing at home with 3 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 3. Dose adjustments may be allowed (Section 8.6.3, Section 8.6.4).

Subjects able to tolerate 300 mg/day for 2 weeks within 40 weeks will begin maintenance treatment (Section 5.2.3.3). Subjects will discontinue early from the study if unable to tolerate 300 mg/day for 2 weeks within 40 weeks, or if the dose level cannot be escalated after 3 consecutive failed attempts (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 5).

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

Dose Number	Study Product Dose (mg)	Interval (weeks)	Increase From Previous Repeated Dose
1	1	2	Not applicable
2	3	2	200%
3	6	2	100%
4	12	2	100%
5	20	2	67%
6	40	2	100%
7	80	2	100%
8	120	2	50%
9	160	2	33%
10	200	2	25%
11	240	2	20%
12	300	2	25%

Up-dosing begins with the first 1 mg/day dose of study product at home.

5.2.3.3 Maintenance Procedures

The maintenance procedures are listed in Appendix 5. The first maintenance visit will occur after 300 mg/day is tolerated for 2 weeks during up-dosing. Maintenance visits will occur every 4 weeks for an overall total of approximately 12 months of treatment. The duration of maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks). Dose adjustments may be allowed (Section 8.6.3, Section 8.6.4).

After the end of maintenance, an exit DBPCFC will be performed (Section 9.2, Appendix 1, Appendix 5). The 300 mg daily dose of study product must be tolerated for at least 2 consecutive weeks before having the DBPCFC.

5.2.4 Unscheduled Visit Procedures

Unscheduled visit procedures are listed in the 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

Early treatment discontinuation is defined as *permanent* cessation of study product administration anytime before completing the exit DBPCFC. Subjects who discontinue early will have early discontinuation procedures approximately 14 days after their last dose of study product according to the schedule of activities (Appendix 5).

Subjects with unresolved adverse events at early discontinuation or who had GI adverse events of interest (Section 8.6.6.2.1) will have safety follow-up per Section 5.5.

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

The primary reasons for early discontinuation of study product are listed in Table 4.

Table 4: Primary Reasons for Early Discontinuation

Category **Reason**	**Comment on Criteria**
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 study 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: – Dose-limiting, moderate, or severe symptoms at any dose on initial dose-escalation day 1 or 2 – Dose withheld for > 4 weeks for chronic or recurrent gastrointestinal adverse events at ≤ 20 mg/day – Unable to tolerate the 300 mg/day dose for 2 weeks within 40 weeks of up-dosing • Use of rescue medications: – Treatment with epinephrine, beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids at any study product dose on initial dose-escalation day 1 or 2

Category **Reason**	**Comment on Criteria**
	– Treatment with epinephrine for a third consecutive time for dose-related allergy symptoms during a dose escalation attempt – Treatment with > 2 doses of epinephrine for a single event of 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 a reduced dose of study product after 3 attempts at dose reduction after mild or moderate allergy symptoms, or unable to tolerate a reduced dose of study product after 1 attempt at dose reduction after severe symptoms – Missed ≥ 15 consecutive days of study product dosing for any reason (eg, as part of the treatment for an intercurrent adverse event), unless the dose was withheld for chronic or recurrent gastrointestinal adverse events at ≤ 20 mg/day. Missed doses per dose adjustment guidelines in Section 8.6.3.2 are allowed.
Use of prohibited medication	Prohibited concomitant medications are listed in Section 7.4.
Death	
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 parent/caregiver preferred the subject 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 > 7 consecutive days (except for management of intercurrent illness) or missed doses for ≥ 3 consecutive days on 3 occasions, unless the dose was withheld for an adverse event or study product dispensing error (Section 8.6.5).
Dropout	
Parent/caregiver or subject decision	Active discontinuation choice by the parent/caregiver or 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 end this study following completion of the study objectives, or earlier if deemed necessary.
Loss to Follow-Up	
Loss to follow-up	Cessation of subject participation without notice or action. Loss to follow-up procedures are described in Section 5.6.

CoFAR, Consortium of Food Allergy Research; IV, intravenous.

5.4 Study Exit

Study exit procedures are listed in Appendix 5. Completion of study exit procedures, including both days of the exit DBPCFC, will be considered as completing the study. The treatment assignment for each subject will be unblinded after study exit and after all major data queries for the subject are resolved.

Eligible subjects will have the option to enroll in an open-label follow-on study to receive AR101 treatment until it becomes commercially available or product development is terminated. If the follow-on study is not yet available at the study site, blinded study treatment may continue and the visit schedule will be every 4 weeks until the follow-on study is available.

Subjects with unresolved adverse events at study exit or who had GI adverse events of interest (Section 8.6.6.2.1) will have safety follow-up per Section 5.5.

5.5 Safety Follow-Up

Safety follow-up procedures are listed in Appendix 6.

Safety follow-up is for subjects with unresolved adverse events at early discontinuation or study exit, or who had GI adverse events of interest (ie, GI adverse events that result in dose interruption > 7 consecutive days or early discontinuation; Section 8.6.6.2.1). The duration of safety follow-up is as follows:

- Subjects who have unresolved adverse events at early discontinuation or study exit will have safety follow-up for at least 30 days or until the ongoing adverse events resolve or stabilize (whichever is last), or until consent for follow-up is withdrawn.
- Subjects who have GI adverse events of interest (Section 8.6.6.2.1) will have safety follow-up for at least 6 months or until consent for follow-up is withdrawn. For chronic or recurrent GI symptoms persisting after 6 months, follow-up will continue for up to 1 year or until chronic or recurrent GI symptoms resolve or consent for follow-up is withdrawn, whichever is first (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 parents/caregivers who do not respond to telephone calls (Section 5.6). Safety follow-up data collected after study database lock will be collected in the safety database.

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

Parents/caregivers of subjects who had GI adverse events of interest (ie, GI adverse events that result in dose interruption > 7 consecutive days or early discontinuation; Section 8.6.6.2.1) 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 the duration of safety follow-up.

In addition, subjects who discontinue early due to GI adverse events will return to the study site monthly for the duration of safety follow-up; 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.

For chronic or recurrent GI symptoms persisting after 6 months, follow-up will continue for up to 1 year or until symptoms resolve or consent for follow-up is withdrawn, whichever is first.

5.6 Loss to Follow-Up

Every reasonable effort must be made to contact the parent/caregiver of 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's parent/caregiver 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 placebo.

The sponsor will provide AR101 and placebo capsules and sachets.

6.2 Study 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.

Placebo is formulated with the same inactive ingredients as AR101 and without peanut flour, and is color-matched with the corresponding AR101 formulation. Placebos will be provided as matching capsules and sachets identical to the AR101 capsules and sachets.

Additional details will be provided in the pharmacy manual.

6.2.1 Packaging of Study Product

Capsules containing study product (AR101 or placebo) 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 are packaged in paperboard cartons (kits) for storage and dispensing to study subjects.

The label will vary depending on individual country requirements.

6.2.2 Storage of Study Product

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 the sponsor and as described in the pharmacy manual. Study sites will maintain temperature logs for storage of study product during the study.

6.2.3 Directions for Administration of Study Product

The first dose at each dose level during up-dosing and at maintenance visits 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 parent/caregiver, 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. Parents/caregivers will be instructed to store the dosing kit in the refrigerator, document all doses taken at home in a diary, and return unused study product and unused kits to the study site at the next visit.

In exceptional circumstances when a subject is unable to return to the study site for the next scheduled visit (eg, travel, holidays) and continued dosing is necessary, an additional dosing kit may be dispensed on a case-by-case basis after submission of a documented request and medical monitor approval. One additional dosing kit may be dispensed to continue the current dose level if there are no safety concerns in the opinion of the investigator and medical monitor (eg, the dose level is tolerated, no intercurrent illnesses) and the subject will have access to appropriate emergency medical services as needed. Up-dosing is not allowed until the next study site 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 with or without fever, or symptoms such as wheezing, worsening asthma, vomiting, or diarrhea, the parent/caregiver is to withhold the dose of study product from the subject and notify the study site of the symptoms and for possible dose adjustments.

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 or the parent/caregiver under direct supervision of study site staff for training purposes. Doses at home will be prepared by the 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 if split. 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 and children are to be observed and supervised by their parents/caregivers for several hours after dosing (including when the subject is napping/sleeping).

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 8.6.3.

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 8.6.5.

Directions for the administration and dispensation of study product may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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). Parents/caregivers will be asked to record daily dosing, reactions to dosing at home, and any doses lost or destroyed at home in the subject's diary and to bring all study product packaging, along with any unused capsules/sachets, to study visits for reconciliation with the diary. Study site personnel must make reasonable efforts to obtain study product packaging and any unused capsules/sachets from parents/caregivers who do not return them at a study site visit.

Treatment compliance procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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 study product 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 study product, 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 corticosteroid use is limited to $\leq$ 3 weeks. Topical steroid use is allowed after an SPT and during the study.

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 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 5.

Table 5: Prohibited Medications

Medication or Treatment	Comment on Use
Angiotensin II receptor blockers	Any use during the study is prohibited.
Angiotensin-converting enzyme inhibitors	Any use during the study is prohibited.
Beta-blockers (oral)	Any use during the study is prohibited.
Calcium channel blockers	Any use during the study is prohibited.
Systemic 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, anticytokine drugs (eg, dupilumab). Before administering a potentially immunomodulatory drug during the study, discuss its use with a medical monitor.
Chronic use of systemic corticosteroids	> 3 consecutive weeks during the study.
Therapeutic immunomodulatory antibodies (experimental or commercially available)	May not be used within 6 months before screening or initiated during the study.
Tricyclic antidepressants	Any use during the study is prohibited.

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 overdose).

Study assessments of safety include adverse events, physical examinations, vital signs, and evaluation of asthma.

Safety procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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 Emergency Procedure for Unblinding Treatment Assignment Due to Adverse Event

An emergency procedure for breaking the blind will be built into the interactive response system. Unblinding of treatment assignment at the study site should occur only if the knowledge will materially change the immediate clinical management of a subject in a medical emergency in the opinion of the investigator.

To unblind a subject's treatment assignment, study site personnel with appropriate permissions will access the unblinding module within the interactive response system. The reason for breaking the blind must be documented in the source documents. The names of the unblinded individuals and the date and time of unblinding must also be documented.

Subjects whose treatment assignment is unblinded will discontinue early from the study and have safety follow-up.

Single patient unblinding may be required for reporting suspected unexpected serious adverse reactions (SUSARs) to certain regulatory authorities. Access to this information will be strictly limited and will not require unblinding at the study site.

8.3 Adverse Event Definitions

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

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding considered clinically significant by the investigator), 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, 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). If a clinically significant abnormality is considered a symptom of a diagnosed condition, then the condition is to be documented as the adverse event

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 related to study product dosing.

Serious adverse events: Any adverse event that meets any of the criteria in Table 6 as determined by the investigator or sponsor.

Table 6: 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 8.5).
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	Not applicable.
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 is reported as an important medical event but is mild or moderate severity and without administration of intensive therapy, 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 8.6.6.

8.4 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.

8.5 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 7).

Table 7: 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 modified EAACI guidelines (Table 8; adapted from Muraro, 2007). The clinical assessment of anaphylaxis is described in Section 8.6.1.1.

Table 8: Modified EAACI Severity Grading System for Anaphylaxis

Severity Grade	Description	Symptoms
1 – Mild	Involves skin and subcutaneous tissues, gastrointestinal, and/or mild respiratory	Flushing; urticaria; periorbital edema or facial angioedema; mild dyspnea, wheeze, or upper respiratory symptoms; mild abdominal pain and/or emesis
2 – Moderate	Involves mild symptoms and features suggesting moderate respiratory, cardiovascular, or gastrointestinal symptoms	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing, and retractions; crampy abdominal pain, recurrent vomiting, and/or diarrhea; and/or mild dizziness
3 – Severe	Involves hypoxia, hypotension, or neurologic compromise	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension [1], confusion, collapse, loss of consciousness, or incontinence

Source: Adapted from Muraro, 2007.

[1] Systolic blood pressure: < 70 mm Hg in subjects aged 1 month to 1 year, < (70 mm Hg + [2 × age]) in subjects aged > 1 to 10 years.

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 9.

Table 9: 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

Source: NCI CTCAE.

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

8.6 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 overdose. 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.

8.6.1 Assessment of Allergic Reactions

Allergy symptoms may occur during treatment with study product 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 and assessment for symptoms of allergic reaction performed 15 to 30 minutes postdose and every approximately 30 minutes thereafter. The postdose observation period during maintenance treatment may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.

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

- Mild symptoms: observe for at least 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 if symptoms are protracted.
- Life-threatening symptoms: observe at an emergency facility for as long as needed consistent with good medical practice. Consider extended overnight observation if symptoms are protracted.

Depending on the subject's stage of development, certain allergy symptoms may be difficult to interpret. Subtle symptoms may include ear picking, tongue rubbing, putting a hand in the mouth, and neck scratching (Bird, 2017). Other symptoms of allergic reaction may include persistent rubbing of the nose or eyes, irritability, clinging to the parent/caregiver, inconsolable crying, somnolence, and drawing legs up to the abdomen.

The assessing physician will determine whether the allergy symptoms meet the criteria for dose-limiting symptoms (Section 8.6.1.2).

The severity of symptoms of an allergic reaction will be assessed as described in Section 8.5.

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

8.6.1.1 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 8.5). Adverse events of anaphylaxis are considered adverse events of interest and require rapid reporting as described in Section 8.7.2.

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, 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, 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:
     - Aged 1 month to 1 year: < 70 mm Hg
     - Aged > 1 to 10 years: < (70 mm Hg + [2 × age])

Potential signs of anaphylaxis in young children may be difficult to interpret because they include behaviors typical for their stage of development, including irritability, clinging to the parent/caregiver, inconsolable crying, and somnolence (Bird, 2017).

8.6.1.2 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 10.

Table 10: Allergy Symptom Severity and Study Product Dose Tolerability

Symptom Severity [1]	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
Life-threatening	Yes	Not tolerated

[1] Depending on the subject's stage of development, allergy symptoms may be difficult to interpret. Age-appropriate allergy symptoms should be considered when assessing the tolerability of a dose.

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.

Life-threatening symptoms: A study product dose associated with life-threatening allergy symptoms will be assessed as not tolerated.

8.6.2 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.

Life-threatening acute allergic reactions will require treatment at an emergency facility as appropriate and consistent with good medical practice.

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.

8.6.3 Dose Adjustment of Study Product for Allergic Reactions

8.6.3.1 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 and/or auscultation).
- 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 (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 11. The same process algorithm for actions to be taken with study product dosing and treatment for acute allergy symptoms is to be followed for allergic reactions occurring on day 2 of initial dose escalation.

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

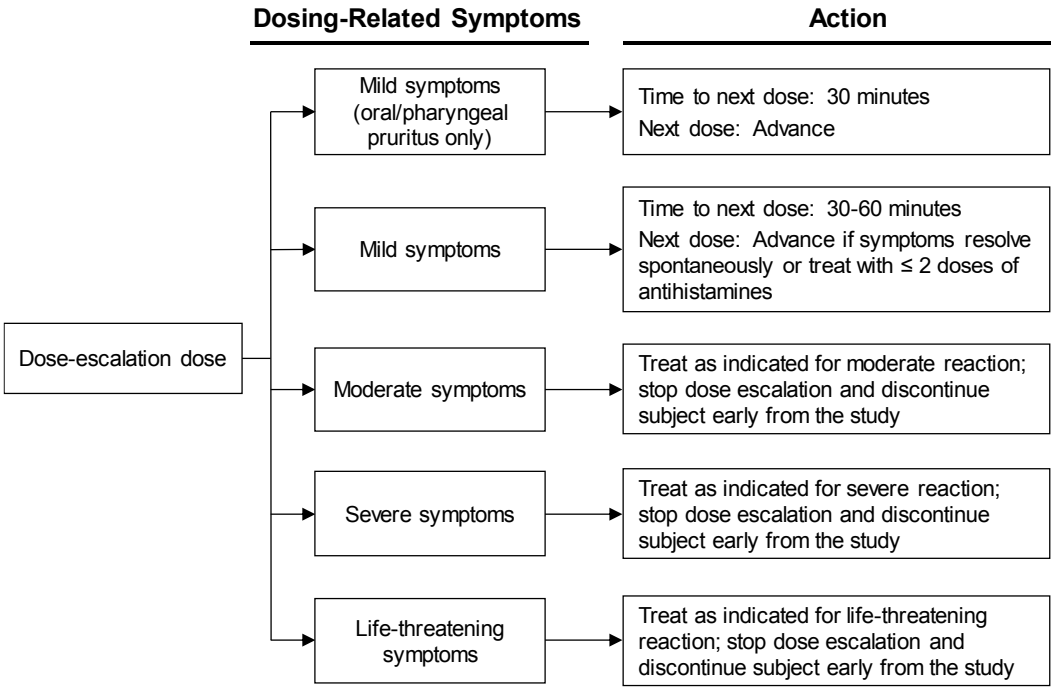


Table 11: Description of Actions to Be Taken With Study Product Dosing for Allergy Symptoms on Initial Dose-Escalation Day 1

Symptoms [1]	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. Treatment may be initiated immediately or after observation. If the first action is observation, observation should not exceed 30 minutes before starting treatment if symptoms have not resolved. Initiate treatment with antihistamines or administer epinephrine immediately as appropriate. Initiate other therapies sequentially or concurrently per investigator judgment. 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.
Life-threatening	For life-threatening symptoms at any dose, administer the appropriate rescue medications and treatment per standard of care. 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, 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).

[1] Depending on the subject's stage of development, allergy symptoms may be difficult to interpret. Age-appropriate allergy symptoms should be considered when determining the appropriate actions to be taken with study product dosing.

8.6.3.2 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 12.

When study product dose-related allergy symptoms occur at home, the parent/caregiver must report the symptoms to the study site to determine whether the next dose should be administered at home or at the study site. 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 8.6.1.2).

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 1 mg.

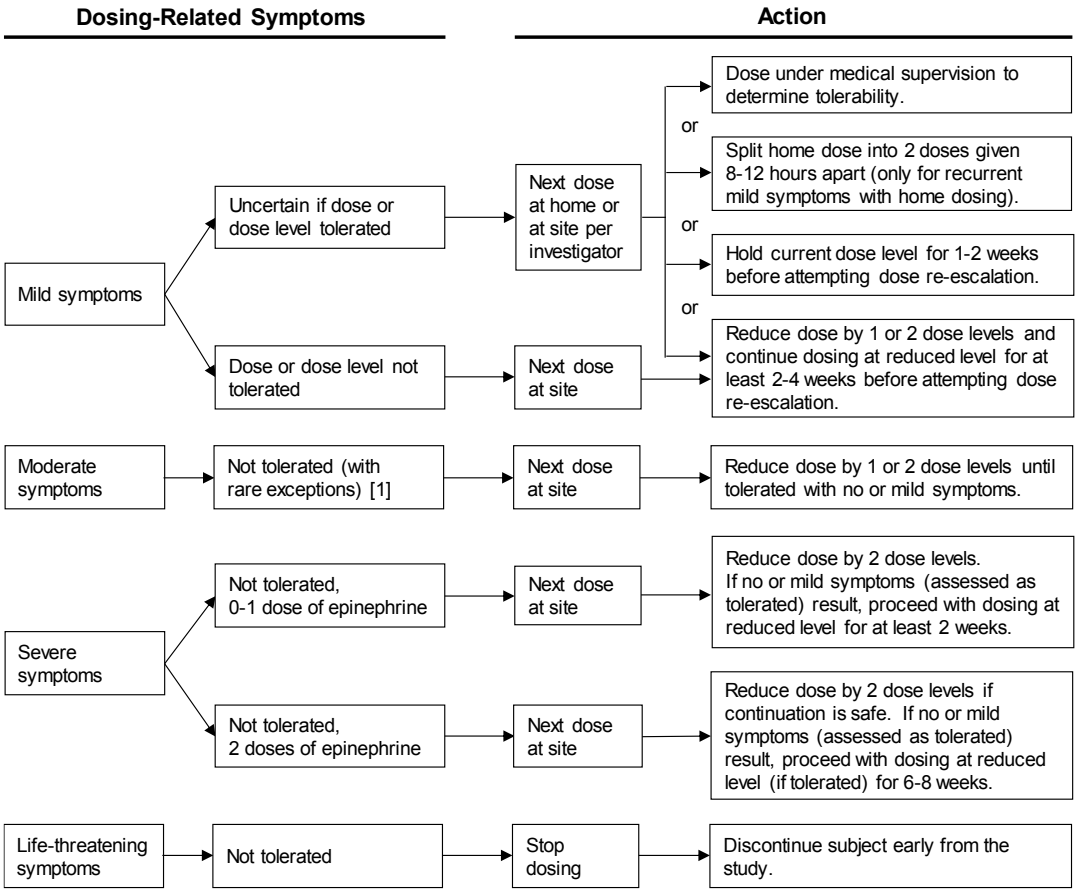
Symptomatic treatment should be used to supplement dose reduction and not as a substitute for it. Symptomatic treatment of adverse events should be discontinued before attempting dose re-escalation at the study site. However, if treatment for chronic or recurrent adverse events cannot be withdrawn successfully, 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 13).

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 reduced dose of study product 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



Assess dose tolerability per Section 8.6.1.2.

[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.

Table 12: Description of Actions to Be Taken With Study Product Dosing for Allergy Symptoms During Up-Dosing and Maintenance

Symptoms [1]	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 8.6.1.2), 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 8.6.1.2), 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 dose 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 8.6.1.2). 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

Symptoms [1]	Actions
	chronic or recurrent GI symptoms at doses ≤ 20 mg/day, withhold study product for 4 weeks and resume at 1 mg/day with the first dose given at the study site. If 1 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).
Life-threatening	Stop study product dosing and discontinue the subject early from the study (Section 5.3).

Assess dose tolerability per Section 8.6.1.2.

[1] Depending on the subject's stage of development, allergy symptoms may be difficult to interpret. Age-appropriate allergy symptoms should be considered when determining the appropriate actions to be taken with study product dosing.

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 is described in Table 13.

Table 13: Dose Adjustment of Study Product After Treatment With Antihistamines and Epinephrine for Dose-Related Allergy Symptoms During Up-Dosing

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 consecutive time for dose-related allergy symptoms during a dose escalation attempt 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, the parent/caregiver is to call emergency medical services and the subject is to be taken 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.

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

The study product dose level may be continued or reduced, or the dose 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.

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 1 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 14. 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 8.6.5).

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 reduced dose of study product cannot be tolerated after 3 attempts to reduce the dose level.

Table 14: Study Product Dose Re-Escalation After Dose Reduction for Reasons Other Than Allergic Reactions

Dose Reductions	Action
1-4 consecutive days	Next dose at the previous dose level under medical supervision at the study site, and continue the 2-week dosing interval.
5-7 consecutive days	Next dose 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	Next dose 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.

8.6.5 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 and allowance for missed consecutive doses of study product during up-dosing and maintenance are described in Table 15.

Table 15: 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, or at approximately 50% (rounded down to the nearest feasible whole dose) at home at investigator discretion.
≥ 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 8.6.3.2).
> 7 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 management of intercurrent illness, or 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 8.6.3.2).
≥ 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 8.6.3.2.

8.6.6 Adverse Events of Interest

Adverse events of interest include anaphylaxis, GI adverse events with prolonged dose interruption (> 7 consecutive days) or that result in early discontinuation, accidental and nonaccidental food allergen exposure, severe adverse events, and use of epinephrine. These events require rapid reporting as described in Section 8.7.2.

Allergic reactions during DBPCFCs will not be considered related to study product or reported as adverse events of interest.

8.6.6.1 Anaphylaxis

The assessment of anaphylaxis is described in detail in Section 8.6.1.1. Adverse events of anaphylaxis are considered adverse events of interest and require rapid reporting as described in Section 8.7.2.

8.6.6.2 GI Adverse Events

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 12). 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.

8.6.6.2.1 GI Adverse Events of Interest

GI adverse events of interest are as follows:

- GI adverse events with prolonged dose interruption, defined as withholding study product for > 7 consecutive days due to GI adverse events anytime during the study, 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

GI adverse events of interest require rapid reporting as described in Section 8.7.2. Parents/caregivers 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 9.4.3.

After early discontinuation or study exit, subjects who had GI adverse events of interest will have safety follow-up as described in Section 5.5.1. Safety follow-up procedures are provided in Appendix 6.

8.6.6.3 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 8.7.2.

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

8.6.6.4 Severe Adverse Events

Adverse events assessed by investigators as severe by any of the 3 severity grading systems (CoFAR for allergic reactions, Table 7; modified EAACI for anaphylaxis, Table 8; or CTCAE for all other adverse events, Table 9) are considered adverse events of interest and require rapid reporting as described in Section 8.7.2. Severe allergy symptoms will result in early discontinuation during initial dose-escalation days 1 and 2 (Table 11) and may result in early discontinuation during up-dosing and maintenance (Table 12).

8.6.6.5 Adverse Events Requiring Use of Epinephrine

Adverse events, especially allergic reactions, may result in epinephrine use, as described in Section 8.6.2. Adverse events requiring use of epinephrine are considered adverse events of interest and require rapid reporting as described in Section 8.7.2.

8.6.7 Overdose

An overdose is defined as any dose of study product greater than the prescribed dose within 1 calendar day. 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.

8.7 Adverse Event Reporting

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

To elicit adverse event reports, 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, subject or parent/caregiver contact with the study site, or during the review of the subject's diary.

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** 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.

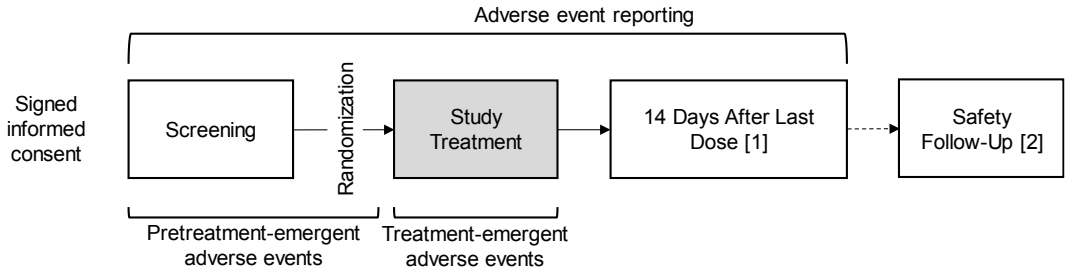
Adverse event terms should include a diagnosis, as available, and is preferred to listing all the individual signs and symptoms. If the diagnosis is not known, the investigator is to record each sign and symptom as an individual adverse event. For multiple symptoms of allergic reactions/hypersensitivity,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

8.7.1 Adverse Event Reporting Period

Collection and reporting of adverse event information will begin at the time the screening informed consent form is signed and assent provided (where required), and will continue for all subjects through 14 days after the last dose of study product or through study exit for subjects receiving AR101 treatment in a follow-on study (Figure 4). Safety follow-up of ongoing adverse events after early discontinuation or study exit will be as follows:

- Subjects with ongoing adverse events will have safety follow-up for at least 30 days or until the adverse events resolve or stabilize (whichever is last), or until consent for follow-up is withdrawn.
- Subjects who have GI adverse events of interest (Section 8.6.6.2.1) will have safety follow-up for at least 6 months or until consent for follow-up is withdrawn. For chronic or recurrent GI symptoms persisting after 6 months, follow-up will continue for up to 1 year or until chronic or recurrent GI symptoms resolve or consent for follow-up is withdrawn, whichever is first.

Figure 4: Adverse Event Reporting Period



[1] Safety data will be collected from signed informed consent and assent (where required) through study exit for subjects receiving AR101 treatment in a follow-on study.

[2] Subjects with unresolved adverse events at early discontinuation or study exit or gastrointestinal adverse events of interest 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.

8.7.2 Reporting for Serious Adverse Events and Adverse Events of Interest

Serious adverse events and adverse events of interest for **all subjects** (ie, both treatment groups) require reporting **without delay** (no longer than 24 hours) following the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study product.

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

- Reporter name and email address
- Details of study treatment
- 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.

8.7.2.1 Serious Adverse Events Reporting

Study site personnel will report serious adverse events to the sponsor or designee using the appropriate case 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 reported information 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).

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

8.7.2.1.1 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.

8.7.2.2 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 8.6.1.1).
- GI adverse events with prolonged dose interruption defined as withholding study product for > 7 consecutive days due to GI adverse events, or GI adverse events that result in early discontinuation (Section 8.6.6.2).
- Accidental/nonaccidental food allergen exposure (Section 8.6.6.3). Rapid reporting is required regardless of whether the exposure resulted in an adverse event.
- Severe adverse events (Section 8.6.6.4). Intended for adverse events that do not meet the criteria for other adverse events of interest.
- Use of epinephrine (Section 8.6.6.5). 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 the appropriate case report form. Adverse events of interest meeting serious adverse event criteria are to be reported as serious adverse events.

9 ASSESSMENT OF EFFICACY AND SAFETY

9.1 Skin Prick Test

Peanut SPT mean wheal diameters and mean erythema diameters will be measured to assess the immunomodulatory effects of study treatment. SPTs will include a positive control (histamine) and negative control (diluent). SPTs for peanut extract will be performed after antihistamines and other medications that could interfere with the assessment of an allergic reaction are discontinued for 5 half-lives of the medication, according to the schedules of activities. Details are provided in the study manual.

9.2 Double-Blind Placebo-Controlled Food Challenge

The screening and exit DBPCFCs will each be conducted over 2 days and are adapted for young children based on accepted food challenge procedures. Single doses of peanut protein and placebo will be conditionally tested at the screening DBPCFC (1, 3, 10, 30, 100, and 300 mg) and exit DBPCFC (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) using a food challenge mixture administered sequentially at 20- to 30-minute intervals up to a single

highest challenge dose of 300 mg at the screening DBPCFC (444 mg cumulative) and 2000 mg at the exit DBPCFC (4043 mg cumulative). The DBPCFC is described in Appendix 1, including all requirements before, during, and after the DBPCFC. Full details are provided in the study manual.

9.3 Palatability Survey

The palatability survey consists of 2 questions and will be used to assess the palatability of study treatment for the subject. The parent/caregiver is to complete the palatability survey.

9.4 Safety and Other Assessments

9.4.1 Assessments of Asthma Control

For subjects with asthma, the evaluation of asthma severity will be assessed using the classification in Table 16.

Asthma control in subjects with pre-existing asthma will be assessed using scores from the Test for Respiratory and Asthma Control in Kids (TRACK) and by the incidence of asthma rescue medication use. The parent/caregiver is to complete the TRACK, a 5-item standardized questionnaire used to evaluate respiratory and asthma control in children aged < 5 years with symptoms consistent with asthma (Zeiger, 2011). Each item is scored on a 5-point scale from 0 (4 or more times a week) to 20 (not at all). Higher scores indicate better respiratory and asthma control.

Table 16: Evaluation of Asthma in Subjects Aged 0 to 4 Years 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	0	1-2 times/month	3-4 times/month	> 1 time/week
Short-acting inhaled beta2-agonist use	≤ 2 days/week	> 2 days/week but not daily	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited

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

9.4.2 Eczema Area and Severity Index

The severity of clinical signs of eczema or atopic dermatitis in subjects with pre-existing eczema or atopic dermatitis will be assessed using the Eczema Area and Severity Index (EASI) scoring system. Higher scores indicate greater severity of eczema or atopic dermatitis.

9.4.3 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 8.6.6.2.1). 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 for Children and Teens. The PEESS v2.0 has not been validated in subjects aged < 2 years.

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.

9.4.4 Physical Examinations and Vital Signs

The investigator will perform physical examinations according to the schedules of activities. Vital signs, weight, and height will also be measured according to the schedules 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, temperature, respiratory rate, and oxygen saturation level. Reference ranges for blood pressure, heart rate, temperature, and respiratory rate in pediatric subjects are provided in Table 17. Investigators are to use the age-specific reference ranges for vital signs to determine whether the vital sign is abnormal and clinically significant.

Table 17: Reference Ranges for Vital Signs in Pediatric Subjects

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

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

[1] Per Sampson, 2006, reduced blood pressure after exposure to a known allergen for the subject (minutes to hours) is as follows:
- Infants and children: > 30% decrease from baseline in systolic blood pressure or low systolic blood pressure in children defined as follows:
  - Aged 1 month to 1 year: < 70 mm Hg
  - Aged > 1 to 10 years: < (70 mm Hg + [2 × age])

10 STATISTICAL METHODS

10.1 Statistical and Analytical Plans

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

Randomization will be central and treatment allocation will be 2:1 (AR101 or placebo). Randomization will be stratified by geographic region (North America, Europe); at least 30% of subjects are planned to be enrolled in Europe.

Data for demographic and baseline characteristics, efficacy, and safety will be summarized by treatment group (AR101 or placebo). 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 of 0.05.

Missing values for efficacy variables will not be replaced or imputed; no interpolation or extrapolation will be applied to missing values unless otherwise specified in the statistical analysis plan.

The statistical methods and statistical analysis plan may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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. The ITT population will be used for all 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 completer population will be defined as all subjects in the ITT population who complete study treatment and have an evaluable exit DBPCFC (completion of at least the peanut food challenge day).

The per protocol population may be defined if it is sufficiently different from the completer population. The per protocol population will include all subjects in the completer population who have no major protocol deviations that may influence the desensitization response.

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). The safety population will be used for all safety analyses and analyzed according to treatment received.

10.3 Determination of Sample Size

A sample size of 132 subjects randomly assigned at a ratio of 2:1 to AR101 (88 subjects) or placebo (44 subjects) provides sufficient power to detect a treatment difference for the primary efficacy analysis for each major health authority region (North America and Europe) (Section 10.5.1).

For North America, the sample size provides 85% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo with an at least 15% margin for the primary efficacy endpoint of the proportion of subjects tolerating an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on the Farrington and Manning method (Farrington, 1990) for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the DBPCFC of 55% in AR101-treated subjects, and a maximum desensitization rate of 15% in placebo-treated subjects, conducted in the ITT population.

For Europe, the sample size provides > 95% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo for the primary efficacy endpoint of the proportion of subjects tolerating an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on the Farrington and Manning method for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the

DBPCFC of 50% in AR101-treated subjects, and a maximum desensitization rate of 10% in placebo-treated subjects, conducted in the ITT population.

The desensitization rates used in the sample size calculations account for an estimated 25% of subjects across both treatment groups to drop out or discontinue early from the study; these subjects will not be replaced and will be considered nonresponders.

Sample size may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

10.4 Interim Analyses

No interim analyses are planned.

10.5 Analysis of Efficacy

10.5.1 Primary Efficacy Analyses

The primary objective assesses the efficacy of AR101 treatment in peanut-allergic subjects aged 1 to < 4 years.

The primary efficacy endpoints are defined by major health authority region.

- **North America:** The primary efficacy endpoint is the proportion of subjects treated with AR101 compared with placebo who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.
- **Europe:** The primary efficacy endpoint is the proportion of subjects treated with AR101 compared with placebo who tolerate an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC.

The ITT population and Farrington-Manning test will be used for these analyses. Subjects tolerating a single dose of at least 600 mg peanut protein for North America and at least 1000 mg peanut protein for Europe will be considered responders; subjects who do not tolerate a single dose of at least 600 mg peanut protein for North America and at least 1000 mg peanut protein for Europe will be considered nonresponders. Nonresponders will also include subjects who withdraw consent or discontinue early anytime before the exit DBPCFC.

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 placebo) will be based on the Farrington-Manning method. The primary efficacy endpoint for North America will be considered met if the lower bound of the 95% CI is greater than the prespecified margin of 0.15. The primary efficacy endpoint for Europe will be considered met if the lower bound of the 95% CI is greater than 0.

10.5.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be assessed in hierarchical order by major health authority region (North America and Europe) if the primary efficacy endpoint analysis is significant at the 0.05 level. Each endpoint will be evaluated for statistical significance (2-sided, $p < 0.05$) only if all preceding in the hierarchy and the primary analysis of the primary efficacy endpoint are statistically significant in favor of AR101. This closed testing procedure maintains the overall type I error rate at 0.05. If any of the preceding tests are not significant, the p-value will be displayed for informational purposes only.

North America:

1. The proportion of subjects who tolerate an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC will be assessed using the ITT population and Farrington-Manning test. 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 placebo) will be based on the Farrington-Manning method.
2. The proportion of subjects who tolerate an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC will be assessed using the ITT population and Farrington-Manning test. 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 placebo) will be based on the Farrington-Manning method.
3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC will be assessed by tabulating the number and percentage of subjects in the ITT population by maximum severity of allergy symptoms at the exit DBPCFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores (row mean score differences statistic) stratified by geographic region will be used to test for a treatment difference.

Europe:

1. The proportion of subjects who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC will be assessed using the ITT population and Farrington-Manning test. 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 placebo) will be based on the Farrington-Manning method.
2. The proportion of subjects who tolerate an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC will be assessed using the ITT population and Farrington-Manning test. 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 placebo) will be based on the Farrington-Manning method.

3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC will be assessed by tabulating the number and percentage of subjects in the ITT population by maximum severity of allergy symptoms at the exit DBPCFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores (row mean score differences statistic) stratified by geographic region will be used to test for a treatment difference.

Full details will be provided in the statistical analysis plan.

10.6 Analysis of Safety

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

Safety data will be collected from signed informed consent and assent (where required) through 14 days after the last dose of study product, or through study exit for subjects receiving AR101 treatment in a follow-on study. Safety follow-up data will be collected for at least 30 days after early discontinuation or study exit for subjects with unresolved adverse events, or for 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 MedDRA. Adverse events will be classified by severity using the CoFAR grading system for allergic reactions, modified EAACI guidelines for anaphylaxis, and CTCAE for all other adverse events (Section 8.5).

Summaries of the safety of AR101 and placebo treatment 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
- Incidence of adverse events during up-dosing and maintenance
- Incidence and severity of treatment-related adverse events
- Incidence of treatment-related adverse events during up-dosing and maintenance
- Incidence of dose modifications
- Exposure-adjusted event rates for the most frequent adverse events (ie, adverse events in ≥ 5% of the safety population)
- Exposure-adjusted event rates for the most frequent treatment-related 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 study treatment 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 TRACK, EASI, 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.

10.7 Analysis of Exploratory Endpoints

Exploratory endpoints will be assessed as follows:

- Change from baseline in peanut-specific and peanut component-specific serum immunoglobulins.
- Change from baseline in mean wheal diameter and mean erythema diameter on SPT to peanut.
- Change from baseline in TRACK and EASI scores.
- Palatability of study treatment, assessed using a palatability survey.
- Proportion of subjects who tolerate a single highest dose of 2000 mg peanut protein (4043 mg cumulative) during the exit DBPCFC.
- Change from baseline in the single highest tolerated dose of peanut protein at the exit DBPCFC.
- Maximum dose of peanut protein reached with no more than mild allergy symptoms at the exit DBPCFC

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

11 STUDY COMMITTEES AND COMMUNICATIONS

An independent, external DSMC will be established to monitor the study for safety. The committee will meet on a periodic basis to review the study safety data in accordance with the DSMC charter.

12 LABORATORY REQUIREMENTS

12.1 Clinical Laboratory Tests

Clinical laboratory tests (hematology, immunology) will be performed according to the schedules of activities (Appendix 4, Appendix 5). 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 18. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements. All clinical laboratory tests required for this study will be performed by the central laboratory specified in Form FDA 1572 Section 4 unless otherwise specified. The central laboratory reference ranges will be used.

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. Example pediatric reference ranges for clinical laboratory tests are provided in Appendix 2. No local laboratory data will be entered into the study database and local laboratories will not be included on Form FDA 1572.

Clinical laboratory test results that are assessed as abnormal and clinically significant are to be documented on the adverse event case report form (Section 8.7). If a clinically significant abnormality is considered a symptom of a diagnosed condition, then the condition is to be documented as the adverse event.

Additional details are provided in the laboratory manual.

Table 18: Clinical Laboratory Tests

Hematology	Immunology
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) Peanut-specific IgG4 and components (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9)

The total volume of blood collected is not to exceed 2 mL/kg per day (maximum 4 mL/kg in a 30-day period) or per local requirements.

12.2 Optional Immune Study to Assess Cellular Responses to Peanut Antigen

Optional blood samples for evaluation of cellular responses to peanut antigen using the basophil activation test (BAT) and mast cell activation test (MAT) will be collected at certain study sites according to the schedules of activities (Appendix 4, Appendix 5). The BAT and MAT will be performed at specified study site laboratories and use flow cytometry to measure CD63 upregulation, a marker of basophil and mast cell activation in IgE-mediated responses to peanut antigen (Santos, 2018; Santos, 2014). The BAT will be conducted in whole blood collected in heparin-containing tubes and tested within 24 hours of collection. Plasma samples will be used to sensitize a mast cell line and mast cell activation in response to peanut antigen will be measured in a flow cytometric assay.

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 and signed Form FDA 1572
- Fully executed clinical trial agreement
- Current curriculum vitae from the investigator (also applies to all subinvestigators listed on the Form FDA 1572)
- Financial disclosure by the investigator (also applies to all subinvestigators listed on the Form FDA 1572)
- 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 investigator or sponsor will obtain confirmation from the EC that the EC is properly constituted and compliant with all requirements and local regulations.

The investigator or sponsor will provide the EC with all appropriate material, such as the protocol, current investigator brochure, site-specific informed consent form, assent form (where required), 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 written informed consent and assent (where required) will be obtained for each subject 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, US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b,c], CFR 50.27, and CFR Part 56, Subpart A), local regulations, and relevant national and international/EU regulations and directives as appropriate by region will be obtained from each 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 and as appropriate per local requirements. 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 document before the investigator implements it.

The investigator will provide a copy of the signed informed consent form and assent form to a subject's parent/caregiver, and will maintain the 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.

Informed consent and assent procedures may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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, in the informed consent form signed by the parent/legal guardian, and in the study participant's assent form (where required).

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.

Study monitoring may be affected by a pandemic, epidemic, or other emergency not related to the study as described in Appendix 3.

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 end 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 Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON)

Signature of Agreement for ARC005 Protocol Amendment 4.0 – 17 Mar 2021

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the principles that have their origin in the Declaration of Helsinki, 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, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

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

Appendix 1: Double-Blind, Placebo-Controlled Food Challenge Procedures

A double-blind, placebo-controlled food challenge (DBPCFC) is a procedure performed under medical supervision by feeding a test food product (containing peanut protein) and placebo in measured, increasing doses on 2 separate days with the subject, parent/caregiver, and study site staff blinded to the randomized order of the challenge days. Study site personnel may not be unblinded to the order of the challenge until after completion of both days of the DBPCFC. The food challenge material will be prepared by a designated unblinded person who is not involved in dosing, monitoring, or assessing the outcome of the DBPCFC. Details for the food challenge material and other DBPCFC procedures are provided in the study manual.

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 a DBPCFC as part of this protocol are described herein; additional procedures may be required as specified in the protocol schedule of activities.

The DBPCFC conducted under this protocol will follow procedures adapted for young children based on the Practical Allergy (PRACTALL) guidelines and guidelines from the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology workgroup (Bird, 2017; Sampson, 2012). The DBPCFC will use the dosing schedule shown in Table 1.

Table 1: Screening and Exit DBPCFC Challenge Doses

Timing	Peanut Protein Dose (mg)	Cumulative Peanut Protein (mg)	
		Screening	Exit
Screening	1	1	0 (or 1) [1]
Screening/Exit	3	4	3 (or 4)
Screening/Exit	10	14	13 (or 14)
Screening/Exit	30	44	43 (or 44)
Screening/Exit	100	144	143 (or 144)
Screening/Exit	300	444	443 (or 444)
Exit	600	-	1043 (or 1044)
Exit	1000	-	2043 (or 2044)
Exit	2000	-	4043 (or 4044)

[1] The 1 mg challenge dose may be administered at the exit DBPCFC per investigator decision.
DBPCFC, double-blind, placebo-controlled food challenge.

PROCEDURES

General Safety Considerations

A study physician will supervise all DBPCFCs.

Personnel involved in a DBPCFC 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 DBPCFC

Before the Day of the DBPCFC

Contact the subject's parent/caregiver: Study site staff should schedule both days of the DBPCFC within 7 days, allowing for the washout period for antihistamines and other medications that could interfere with the assessment of an allergic reaction, 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. The timing of the challenge should coincide with a normal meal time for the subject; avoid scheduling the challenge during a usual naptime for the subject. Study site staff will contact the subject's parent/caregiver in advance of the scheduled days of the DBPCFC to communicate the following:

- Review the events of the day (eg, study procedures, modality of the DBPCFC, 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 DBPCFC will be rescheduled in case of illness or symptoms such as wheezing, fever, vomiting, and diarrhea; the parent/caregiver is to notify the study site if such symptoms develop before the DBPCFC.
- Confirm 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 DBPCFC assessment for 5 half-lives of the medication before the DBPCFC 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 DBPCFC. A light meal (half the subject's usual amount) may be given 2 hours before the DBPCFC.
- Instruct that the dose of study product is to be withheld on the days of the exit DBPCFC.

On the Day of the DBPCFC

1. Check the protocol schedule of activities and complete any required procedures as specified before starting the DBPCFC.
2. Confirm the following:
   - Subject has not received study product.
   - No recent or active illnesses. Reschedule the DBPCFC if the subject is experiencing symptoms of an acute infection (eg, wheezing, coughing, fever, recent nausea, vomiting, diarrhea, ear infection) or any other illness that may interfere with the subject's safety or interpretation of the results. Do not conduct the DBPCFC if illness is suspected.
   - Control of chronic atopic diseases. Do not proceed with the DBPCFC if the subject is experiencing unstable or exacerbated atopic disease such as asthma, atopic dermatitis, urticaria, or allergic rhinitis. Reschedule the DBPCFC 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 DBPCFC for 5 half-lives of the medication before the challenge day.
3. Measure baseline vital signs (blood pressure, heart rate, temperature, respiratory rate, oxygen saturation level) and body weight.
4. Perform a physical examination to confirm adequate baseline, including the ears, oropharynx, nose, lungs, and skin.
5. 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.
6. 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.
7. Inform that the subject, parent/caregiver, and study site personnel (except the unblinded person preparing the food challenge material) will be blinded to the order of the challenge days, and will not be unblinded to the order until the end of observations on the second day.

PREPARATION OF DBPCFC MATERIAL

The designated unblinded person will access the interactive response system to obtain the randomization order for the peanut protein and placebo challenge days, and prepare the DBPCFC material for each day according to the instructions in the study manual. Potentially

unblinding information (eg, labeled packaging, mixing containers, worksheets) must be stored in a secure location before the dosing containers are given to the blinded study staff to administer to the subject.

DOSING AND MONITORING DURING THE DBPCFC PROCEDURE

Before Each Dose of the DBPCFC

1. Measure and record vital signs (blood pressure, heart rate, temperature, respiratory rate, oxygen saturation level).
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 ears, 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. Carefully observe for objective signs of an allergic reaction.
3. Progress to the next challenge 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 (and parent/caregiver) is willing.
4. Doses may not be repeated in this DBPCFC.

Signs and Symptoms During the DBPCFC

At each challenge dose 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 symptoms during food challenges meet the criteria for dose-limiting symptoms. When practicable, the same assessing physician will evaluate symptoms for the same subjects during both days (peanut protein and placebo challenges) of both the screening and exit DBPCFCs; however, the same assessing physician must evaluate symptoms for the same subjects during both days of the exit DBPCFC.

To maintain the blind, the assessing physician may not be involved in preparing the food challenge doses or become unblinded to the food challenge materials before the observation period is complete on the second day of the DBPCFC. The assessing physician during the exit DBPCFC may not be involved with the treatment of the subject during the study, such as study product dosing or assessment of adverse events. If the assessing physician at the screening DBPCFC becomes involved in the treatment of the subject, then another assessing physician must evaluate symptoms for the subject during the exit DBPCFC.

Allergy symptoms may be difficult to interpret depending on the subject's stage of development. Subtle symptoms may include ear picking, tongue rubbing, putting a hand in the mouth, and neck scratching (Bird, 2017). The assessing physician is to use the suggested guidelines in Table 2 or Table 3 as appropriate for the subject's stage of development.

Table 2: Food Challenge Stopping Criteria for Subjects Aged 1 to < 4 Years

Major Criteria (stop food challenge if ≥ 1 criteria are present)	**Minor Criteria (stop food challenge if ≥ 2 criteria are present)**
• Confluent erythematous, pruritic rash • ≥ 3 urticarial lesions • ≥ 1 site of angioedema • Respiratory (at least 1 of the following): – Wheezing – Repetitive cough – Difficulty breathing or increased work of breathing – Stridor – Dysphonia – Aphonia • Hypotension for age not associated with vasovagal episode • Evidence of severe abdominal pain (eg, abnormal stillness, inconsolable crying, doubling over/drawing legs up to the abdomen) persisting ≥ 3 minutes	• Vomiting (except gag reflex-induced vomiting during feeding) • Diarrhea • Persistent rubbing of nose or eyes ≥ 3 minutes • Persistent rhinorrhea ≥ 3 minutes • Persistent scratching ≥ 3 minutes

Source: Adapted from the Learning Early About Peanut Allergy (LEAP) study protocol and guidelines from the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology workgroup (Bird, 2017; Du Toit, 2015).

Symptoms should be of new onset and must occur within 2 hours after the last dose. Quantitative criteria (eg, persistent scratching ≥ 3 minutes) are continuous, not cumulative during the entire double-blind, placebo-controlled food challenge.

The food challenge will be considered positive if ≥ 1 major criteria or ≥ 2 minor criteria are present.

The food challenge will be considered indeterminate if 1 minor criterion is present at the time the food challenge is stopped (ie, onset of the first minor symptom does not meet the food challenge stopping rules).

The food challenge will be considered negative if both major and minor criteria are absent.

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)

Source: Adapted from Practical Allergy (PRACTALL) guidelines (Sampson, 2012).

Recommended actions for subjects experiencing allergy symptoms are as follows:

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

- **Stop the DBPCFC, 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 dose level of the DBPCFC is positive.

- **Stop the DBPCFC, 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 severe 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 DBPCFC 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 DBPCFC 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, or if an allergic reaction is suspected but objective symptoms are not yet present. In this case:

- Close observation is mandatory.
- Measure vital signs (blood pressure, heart rate, temperature, respiratory rate, oxygen saturation level) 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 DBPCFC due to subjective symptoms or if the subject or parent/caregiver refuses to proceed (eg, due to significant anxiety) even if no objective allergy symptoms are documented.

DBPCFC OUTCOMES AND TREATMENT / OBSERVATION

Negative DBPCFC

Observe the subject for 2 hours after the last dose. Vital signs may be measured during the 2-hour observation period at investigator discretion and must be measured at the end of the 2-hour observation period. Release the subject if no symptoms are detected by the end of the 2-hour observation period after the last dose.

Positive DBPCFC

Treatment of subjects with symptoms: Treat subjects with any symptoms elicited by the DBPCFC per the accepted medical practices at the study site. Record all treatments administered for allergic reactions during a DBPCFC 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, respiratory rate, oxygen saturation level) until releasing the subject. Suggested timing:
   - Approximately 15-minute intervals until symptoms resolve
   - Approximately 30 and 60 minutes after symptoms resolve
   - Hourly until releasing the subject
   - At release (end of observation)
3. 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.
4. 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.
5. Generally, if the emergence of allergy symptoms halts the DBPCFC, 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 DBPCFC is halted (eg, due to anxiety or refusal to continue) and symptoms are mild and not considered to be dose-limiting.
   - Depending on the subject's stage of development, the reason for anxiety or refusal to continue may be difficult to interpret, as these could be signs of an allergic reaction (eg, stomach pain). When the DBPCFC is halted for uninterpretable reasons, record it as such on the case report form.

POST-DBPCFC INSTRUCTIONS AND FOLLOW-UP

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

1. The subject may resume eating and drinking without restrictions 30 minutes after the last challenge dose is administered.
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 the 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-DBPCFC adverse events, and assist accordingly.

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Appendix 2: Example Clinical Laboratory Test Pediatric Reference Ranges

The central laboratory reference ranges will be used for the clinical laboratory tests required for this study.

Example pediatric reference ranges for clinical laboratory tests are provided in the following tables as a guide (Hughes, 2018). A limitation of the example reference ranges is the small sample sizes of patients in many studies that were used to derive the ranges; therefore, caution should be used in their interpretation. Reference values for clinical laboratory tests vary depending on the analytical method used. Therefore, investigators are to use the age-specific reference ranges from the local laboratory to determine whether a test result is abnormal and clinically significant.

Table 1: Example Blood Chemistry Reference Ranges

Analyte	Conventional Units	International System of Units (SI)
Alanine aminotransferase (ALT)		
1-3 years	5-45 U/L	5-45 U/L
4-6 years	10-25 U/L	10-25 U/L
Alkaline phosphatase		
Infant	150-420 U/L	150-420 U/L
2-10 years	100-320 U/L	100-320 U/L
Aspartate aminotransferase (AST)		
10 days-24 months	9-80 U/L	9-80 U/L
> 24 months		
Female	13-35 U/L	13-35 U/L
Male	15-40 U/L	15-40 U/L
Bilirubin (total)		
Infant (> 5 days) – preterm	< 2 mg/dL	< 34 µmol/L
Infant (> 5 days) – term	< 1.2 mg/dL	< 21 µmol/L
Adult	< 1.5 mg/dL	< 20.5 µmol/L
Bilirubin (conjugated)		
Infants/children	< 0.2 mg/dL	< 3.4 µmol/L
Blood urea nitrogen (BUN)		
Infant/child	5-18 mg/dL	1.8-6.4 mmol/L
Calcium (total)		
10 days-24 months	9.0-11.0 mg/dL	2.25-2.75 mmol/L
24 months-12 years	8.8-10.8 mg/dL	2.2-2.7 mmol/L
Calcium (ionized)		
1-18 years	4.9-5.5 mg/dL	1.22-1.37 mmol/L
Carbon dioxide ($PaCO_2$)		
Child/adult	32-48 mmHg	

Analyte	Conventional Units	International System of Units (SI)
Chloride (serum)		
6-12 months	97-106 mEq/L	97-106 mmol/L
Child/adult	97-107 mEq/L	97-107 mmol/L
Cholesterol (total)		
Child/adolescent		
Desirable	< 170 mg/dL	
Borderline	170-199 mg/dL	
High	> 200 mg/dL	
Creatine kinase (creatine phosphokinase)		
> 6 weeks-adult male	20-200 U/L	20-200 U/L
> 6 weeks-adult female	20-180 U/L	20-180 U/L
Creatinine (serum, enzymatic)		
Infant	0.2-0.4 mg/dL	18-35 µmol/L
Child	0.3-0.7 mg/dL	27-62 µmol/L
Gamma-glutamyl transferase (GGT)		
4 months-10 years	5-32 U/L	5-32 U/L
Glucose (serum)		
Newborn, > 1 day	50-90 mg/dL	2.8-5.0 mmol/L
Child	60-100 mg/dL	3.3-5.5 mmol/L
Lactate dehydrogenase (at 37°C)		
10 days-24 months	180-430 U/L	180-430 U/L
24 months-12 years	110-295 U/L	110-295 U/L
Phosphorus		
10 days-24 months	4-6.5 mg/dL	1.29-2.10 mmol/L
3-9 years	3.2-5.8 mg/dL	1.03-1.87 mmol/L
Potassium		
Infant	4.1-5.3 mEq/L	4.1-5.3 mmol/L
Child	3.4-4.7 mEq/L	3.4-4.7 mmol/L
Proteins (protein electrophoresis)		
Total		
15 days-1 year	5.1-7.3 g/dL	
1-2 years	5.6-7.5 g/dL	
3-16 years	6.0-8.0 g/dL	
Albumin		
15 days-1 year	2.2-4.8 g/dL	
1-2 years	3.6-5.2 g/dL	
3-16 years	3.6-5.2 g/dL	
Sodium		
> 1 year	135-147 mEq/L	135-147 mmol/L

Analyte	Conventional Units	International System of Units (SI)
Triglycerides (total)		
1-3 years male	27-125 mg/dL	0.31-1.41 mmol/L
1-3 years female	27-125 mg/dL	0.31-1.41 mmol/L
4-6 years male	32-116 mg/dL	0.36-1.31 mmol/L
4-6 years female	32-116 mg/dL	0.36-1.31 mmol/L
Uric acid		
1-12 months	1.1-5.6 mg/dL	0.065-0.33 mmol/L
1-5 years	1.7-5.8 mg/dL	0.1-0.35 mmol/L

Source: Adapted from Hughes, 2018.

Table 2: Example Hematology Reference Values

Blood Cell Indices	Age	
	6 Months-2 Years	2-6 Years
Hemoglobin, g/dL [1]	12.0 (10.5)	12.5 (11.5)
Hematocrit, % [1]	36 (33)	37 (34)
Mean corpuscular hemoglobin concentration, g/dL RBC [1]	33.0 (30.0)	34.0 (31.0)
Mean corpuscular volume, fL [1]	78 (70)	81 (75)
Reticulocytes	–	(0.5-1.0)
White blood cell, $\times 10^3$/mL [2]	10.6 (6-17)	8.5 (5-15.5)
Platelets, $\times 10^3$/mL [2]	(150-350)	(150-350)

Source: Adapted from Hughes, 2018.
[1] Data are mean (-2 SD).
[2] Data are mean ((±2 SD).
RBC, red blood cell.

Table 3: Example Leukocyte Differential

Age	Total Leukocytes [1]	Neutrophils [2]		Lymphocytes		Monocytes		Eosinophils	
	Mean (Range)	Mean (Range)	%	Mean (Range)	%	Mean	%	Mean	%
1 year	11.4 (6-17.5)	3.5 (1.5-8.5)	31	7.0 (4-10.5)	61	0.6	5	0.3	3
2 years	10.6 (6-17)	3.5 (1.5-8.5)	33	6.3 (3-9.5)	59	0.5	5	0.3	3
4 years	9.1 (5.5-15.5)	3.8 (1.5-8.5)	42	4.5 (2-8)	50	0.5	5	0.3	3
6 years	8.5 (5-14.5)	4.3 (1.5-8)	51	3.5 (1.5-7)	42	0.4	5	0.2	3

Source: Adapted from Hughes, 2018.
Ranges are estimates of 95% confidence limits and percentages refer to differential counts.
[1] Numbers of leukocytes are $\times 10^3/\mu L$.
[2] Neutrophils include band cells.

Table 4: Example Urinalysis Normal Findings

Urinalysis	Normal Finding
Appearance	Clear to cloudy
Bilirubin	Negative
Color	Almost colorless to amber
Glucose	Negative
Ketones	Negative
Nitrite	Negative
pH	4.5-8
Protein	Negative
Specific gravity	1.003-1.030
Urobilinogen	Normal

Source: Adapted from Hughes, 2018.

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Appendix 3: Guidance on Study Conduct During a Pandemic, Epidemic, or Other Emergency Not Related to the Study

Table of Contents

1 INTRODUCTION

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

Study sites must inform Aimmune (study sponsor) as soon as possible when such restrictions are issued or anticipated. Similarly, study sites must inform the sponsor when the restrictions are lifted. The resumption of study site visits will be determined in consideration of individual subjects; study sites; and local, state, regional, and national guidance as applicable; and in accordance with regulatory requirements.

The alternate procedures (also referred to as remote procedures) described in this appendix may be implemented for individual subjects; by study site; or at the local, state, regional, or national level as appropriate. As the ability to attend scheduled study site visits may change over time for individual subjects, study visits may alternate between remote procedures and study site visits as needed for flexibility until the restrictions are fully lifted and regular study site visits can resume. Additional details for the remote procedures will be provided in other supporting documents for study conduct. Procedures will be per protocol for subjects able to attend scheduled visits at the study site.

This appendix was prepared in consideration of the guidance released by the Food and Drug Administration (FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency updated 11 May 2020) and the European Medicines Agency (Guidance on the Management of Clinical Trials During the COVID-19 [Coronavirus] Pandemic version 3, 28 Apr 2020). As updates to these regulatory guidances are expected, the alternate procedures described in this appendix may be supplemented or superseded accordingly through supportive materials for study conduct as directed by the sponsor.

2 ENROLLMENT AND STUDY PROCEDURES

2.1 Recruitment, Screening, and Enrollment

The sponsor will notify study sites when recruitment, screening, and enrollment of subjects is suspended.

An exception to suspension of screening and enrollment is as follows: subjects who complete the first day of the screening double-blind, placebo-controlled food challenge (DBPCFC) before remote procedures are implemented may return to the study site to complete the second day of the DBPCFC per protocol and enroll in the study if eligible. However, continued participation in the study will be per investigator and parent/caregiver decision, based on the ability to attend study site visits and understanding the potential impact of the restrictions on study conduct.

The sponsor will notify study sites when recruitment, screening, and enrollment may resume. Rescreening may be considered for subjects who did not complete screening procedures, including those not starting screening food challenges, and for subjects who were enrolled in the study but did not start treatment due to the restrictions. Rescreening requires medical monitor approval and will be conducted per protocol.

2.2 Informed Consent

Study site personnel must obtain consent and assent (where required) before any remote procedures or rescreening procedures are conducted. Consent for remote procedures will include the release of contact information to allow the shipment of study product directly to the subject or designated responsible person’s home or for study product to be picked up at the study site. Reconsent for other reasons (eg, protocol amendment, updated safety information) may be required during the restrictions.

The informed consent process (written; oral if the return of written consent for remote procedures is not possible) must be documented in the subject's source documents. Written consent is to be returned to the study site as soon as feasible for subjects who provided oral consent.

2.3 Duration of Study

The total duration of the study and duration of study treatment for individual subjects will be extended as needed to allow subjects to complete study treatment following delays due to the restrictions.

2.4 General Study Visit Procedures

Study visits will be conducted remotely (eg, telephone or video call) for subjects, parents, and caregivers who cannot attend scheduled visits at the study site due to the restrictions. Remote study visits will occur at the same intervals specified in the protocol schedules of activities.

On the day of a remote study visit, subjects will take their dose of study product at home per their usual dosing schedule.

During remote study visits, noninterventional visit procedures will be conducted according to the protocol schedules of activities as applicable and recorded in the subject's source documents:

- Adverse events review
- Concomitant medications review and instruction
- Treatment compliance/accountability review
- Diet/food allergen exposure review
- Food allergy instruction
- Asthma evaluation for subjects with asthma

Procedures that will <u>not</u> be completed during remote study visits are as follows:

- Weight, height, and vital signs measurements
- Questionnaires to assess atopic disease
  - Test for Respiratory and Asthma Control in Kids (TRACK)
  - Eczema Area and Severity Index (EASI)
- Physical examinations
  - Skin prick tests
  - Blood sample collection
- Food challenges
  - Food challenges will be delayed until the restrictions are lifted and regular study site visits resume. Food challenges are to be completed within 3 months after

regular study site visits resume for subjects who meet the protocol criteria for having a food challenge.

After completion of a remote study visit, study product will be dispensed as needed for dosing at home. Study site staff should confirm that study product was received by the appropriate individual.

After each remote study visit, site staff will contact the parent/caregiver by telephone within 3 days. In addition to the standard telephone call queries, receipt of study product will be confirmed (if applicable). The telephone call is at investigator discretion when study product is not dispensed after a remote study visit and dosing is continued at the same dose level.

2.4.1 Initial Dose Escalation

Subjects who completed day 1 but not day 2 of initial dose escalation at the time remote procedures were implemented will stop study product dosing until regular study site visits resume. When study site visits resume, day 1 of initial dose escalation will be repeated following discussion and approval from the medical monitor (Section 4.2).

2.4.2 Up-Dosing Period

The duration of up-dosing for individual subjects will be extended to accommodate any delays due to the restrictions.

Subjects in the up-dosing period of study treatment will continue daily dosing with study product at their current dose level until the next study site visit. Dose adjustments may be allowed (Section 4.1, Table 1). No up-dosing will be allowed until the next study site visit.

When study site visits resume, study treatment will continue or resume under medical supervision at the study site as follows:

- Subjects who continued dosing at their current dose level or a lower dose level may resume up-dosing to the next dose level at the study site per protocol.
- Subjects who stopped study product and did not discontinue from the study may reinitiate dosing at the study site following approval from the medical monitor as described in Section 4.2, Table 1, and Table 2.

2.4.3 Maintenance Period

The duration of maintenance treatment for individual subjects will be extended as needed to accommodate any delays due to the restrictions.

Subjects in the maintenance period of study treatment will continue daily dosing at their current dose level of study product until study site visits resume. Dose adjustments may be allowed (Section 4.1, Table 1).

When study site visits resume, study treatment will continue or resume under medical supervision at the study site as follows:

- Subjects who continued daily dosing at 300 mg/day may continue their maintenance treatment regimen per protocol.
- Subjects who had dose reductions during the maintenance period will follow dose re-escalation procedures per protocol.
- Subjects who stopped study product and did not discontinue from the study may reinitiate dosing at the study site following approval from the medical monitor as described in Section 4.2, Table 1, and Table 2.

2.5 Remote Unscheduled Visits

Unscheduled visits may be performed remotely anytime to assess or follow up adverse events or at the request of the parent, caregiver, or investigator, or if additional study product is needed before the next scheduled remote study visit. The date and reason for the remote unscheduled visit must be recorded in the source documentation.

Noninterventional unscheduled visit procedures will be conducted as appropriate according to the protocol schedules of activities and the data recorded in the subject's source documents.

2.6 Early Discontinuation

Subjects who discontinue early from the study while restrictions are in place will have a remote early discontinuation visit approximately 14 days after their last dose of study product. Noninterventional early discontinuation procedures will be conducted according to the protocol schedule of activities and as described in Section 2.4. Parents/caregivers will be encouraged to bring subjects back to the study site to complete all early discontinuation procedures when regular study site visits resume, unless consent is withdrawn.

Subjects with unresolved adverse events at early discontinuation while restrictions are in place or who had gastrointestinal (GI) adverse events of interest will have safety follow-up (Section 2.8).

The criteria for early discontinuation due to missed doses while restrictions are in place will be based on the guidance provided later in this appendix (Figure 1, Table 1). Depending on the reason and number of missed doses, certain subjects who miss doses and stop study product dosing when the restrictions are in place will not be discontinued early from the study. Such subjects may reinitiate dosing after study site visits resume. When regular study site visits resume, the regular protocol criteria for early discontinuation due to missed doses will apply.

2.7 Study Exit

Subjects who complete study treatment (initial dose escalation, up-dosing, and maintenance, which may be extended when restrictions are in place) will continue blinded study treatment and have remote study visits every 4 weeks until regular study site visits resume. Study exit will not occur until regular study site visits resume. Study exit procedures will be conducted in accordance with the study protocol.

2.8 Safety Follow-Up

In the event remote procedures are implemented, safety follow-up procedures will be conducted in accordance with the study protocol, except that subjects who discontinue due to GI adverse events will have remote study visits instead of study site visits when required, and no symptom-directed physical examinations will be performed.

Parents/caregivers of subjects who had GI adverse events of interest will be asked to complete the Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0) per protocol.

3 TREATMENT COMPLIANCE

Accountability for the study product will be performed to document compliance with the dosing regimen. During remote study visits, parents/caregivers will be asked to return the study diary, all used study product packaging, and any unused capsules/sachets to the study site. If the return of these items is not feasible until the next study site visit, parents/caregivers will be asked to send photographs of the study diary (relevant pages), used study product packaging, and unused capsules/sachets to the study site for interim reconciliation with the study diary. Physical study product accountability and reconciliation with the study diaries will be performed after the materials are received at the study site. New study diaries will be dispensed as needed following completion of a remote study visit. Used study product packaging and unused capsules/sachets will not need to be stored at 2°C to 8°C.

Parents/caregivers will be asked to bring study diaries, used study product packaging, and unused capsules/sachets to the next study site visit if the return of these items to the study site is not feasible while restrictions are in place. Study site personnel must make reasonable efforts to obtain these items from parents/caregivers who do not return them at the next study site visit.

4 SAFETY CONSIDERATIONS

4.1 Dose Adjustment

The study product dose level may be continued or reduced, or the dose withheld per investigator judgment based on considerations including allergy symptoms, flare of atopic

disease unrelated to study product, intercurrent illness, treatment period (up-dosing vs maintenance), and access to local medical services.

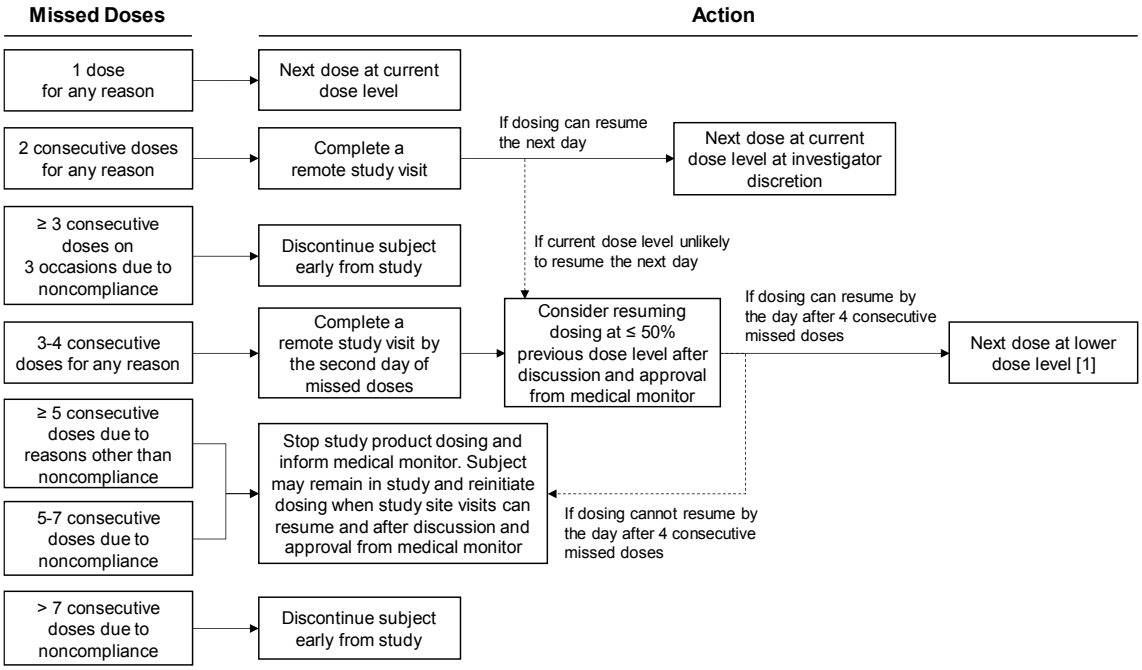
The decision to reduce a dose level when a study site visit is not possible requires discussion and approval from the medical monitor and should occur as soon as possible to ensure timely dispensation of the study product. The reduced dose level will continue until study site visits resume and dose re-escalation can be attempted under medical supervision at the study site.

4.2 Missed Doses

Parents/caregivers will be instructed to contact the study site by the second day of consecutive missed doses if a second consecutive missed dose is anticipated. A remote unscheduled visit will be conducted to determine the reason for the missed doses (eg, adverse events, noncompliance) and to assess the safety of resuming the next dose at home. Access to local medical services should also be considered. The decision to resume study product dosing at a lower dose level after at least 2 consecutive missed doses should be made as soon as possible following discussion and approval from the medical monitor. If the consecutive missed doses were due to allergic adverse events and the dose level is assessed as not tolerated, dosing at the same dose level should not resume until regular study site visits resume.

Procedures for missed consecutive doses of study product when study site visits cannot be conducted are described in Figure 1 and Table 1. Subjects who stop study product dosing and do not discontinue early from the study may reinitiate dosing under medical supervision at the study site after study site visits resume and following discussion and approval from the medical monitor as described in Table 2. Until study site visits resume, unscheduled visits should be performed monthly to review adverse events and concomitant medications (at minimum).

Figure 1: Procedures for Missed Consecutive Doses of Study Product



The guidance for 1 missed dose or 2 missed consecutive doses assumes that the current dose level is assessed as tolerated if dosing is continued at the current dose level.

[1] At investigator discretion, the subject may be observed by video call during and after administration of the next dose of study product at home.

Table 1: Description of Actions for Missed Consecutive Doses of Study Product

Missed Doses	Action
1 dose for any reason [1]	Resume next dose at current dose level at home.
2 consecutive doses for any reason [1]	Complete a remote study visit by the second consecutive day a dose is anticipated to be missed. If dosing can resume the next day, resume next dose at current dose level at home at investigator discretion. If a third consecutive dose is likely to be missed, follow action for missing 3 consecutive doses for any reason.
3-4 consecutive doses for any reason	Complete a remote study visit by the second consecutive day a dose is anticipated to be missed. Consider resuming next dose at ≤ 50% of previous dose (rounded down to the nearest feasible whole dose) at home if considered safe and following discussion and approval from the medical monitor. At investigator discretion, the subject may be observed by video call during and after administration of the next dose of study product. If continued dosing is assessed as not safe or dosing cannot resume by the day after 4 consecutive missed doses, stop study product dosing and inform the medical monitor. Subject may remain in the study and reinitiate dosing when study site visits can resume and following discussion and approval from the medical monitor.

Missed Doses	Action
≥ 3 consecutive doses on 3 occasions due to noncompliance	Stop study product dosing and discontinue the subject early from the study.
5-7 consecutive doses due to noncompliance ≥ 5 consecutive doses due to reasons other than noncompliance (eg, adverse event, epidemic- or pandemic-related reasons)	Stop study product dosing and inform the medical monitor. Subject may remain in the study and reinitiate dosing when study site visits can resume and following discussion and approval from the medical monitor.
> 7 consecutive doses due to noncompliance	Stop study product dosing and discontinue the subject early from the study.

[1] The guidance assumes that the current dose level is assessed as tolerated if dosing is continued at the current dose level.

Table 2: Reinitiation of Study Treatment After Stopping Study Product

Number of Days Since Last Dose	Action [1]
≤ 14 days during any period	Resume dosing per protocol [2]
> 14 days during initial dose escalation	Reinitiate dosing from initial dose escalation day 1
15-30 days during up-dosing or maintenance	Reinitiate up-dosing at 1 mg
> 30 days during up-dosing or maintenance	Reinitiate dosing from initial dose escalation day 1

Resumption of dosing under medical supervision at the study site requires discussion and approval from the medical monitor.

[1] Additional procedures for subjects who stopped study product dosing for > 14 days are as follows:
- Confirm that the subject has no clinically significant change in health status (eg, severe or uncontrolled asthma, eosinophilic esophagitis or other eosinophilic gastrointestinal disease, chronic or recurrent gastrointestinal adverse events of unknown etiology) or any other health condition that would preclude participation in the study, in the opinion of the investigator.
- Obtain medical monitor approval before reinitiating dosing.
- When up-dosing is reinitiated, dose escalation may resume per protocol.

[2] Subjects who completed day 1 but not day 2 of initial dose escalation at the time remote procedures were implemented will repeat day 1 of initial dose escalation.

5 STATISTICAL METHODS

Changes to the statistical methods and data presentations for reporting the study due to any restrictions will be detailed in the statistical analysis plan.

Limits to the prespecified maximum duration of up-dosing and maintenance periods for subjects to meet the criteria of responders at the exit food challenge will continue to apply, with the exception of any duration of time affected by the restrictions as defined by the first and last consecutively affected study visits. For instances of multiple distinct durations of

restriction, the maximum duration of the up-dosing and maintenance periods will be extended by the cumulative sum of these distinct durations of affected study visits.

Subjects who discontinue early from the study for any reason before completing their scheduled exit food challenge, including due to the restrictions, will be counted as nonresponders in an intent-to-treat analysis, and may also be excluded from an alternative sensitivity analysis of the primary and prespecified secondary endpoints as appropriate.

Additional subjects may need to be enrolled to accommodate a potential increase in dropouts, a substantial extension of the up-dosing period, or a substantial delay in completion of exit food challenges. In the event a greater than anticipated number of subjects discontinue early from the study due to the restrictions, the study sample size may be increased by up to 20% without protocol amendment. The sponsor may perform one or more blinded sample size reassessments, potentially in consultation with an external unblinded data and safety monitoring committee, to address any safety concerns associated with an increase in the study sample size.

6 STUDY MONITORING

Study monitoring will be conducted remotely until onsite study monitoring visits can resume.

Appendix 4: Study Schedule of Activities: Screening (Days -42 to -1)

Activity	Comments
General	Complete screening procedures within 42 days after obtaining signed consent (and assent where required).
Informed consent, subject ID number	Obtain consent (and assent where required) before performing any study-specific procedures. Ensure consent is on current version of form reviewed by the ethics committee.
Questionnaire	Instruct parent/caregiver to complete TRACK (for subject with asthma) before the DBPCFC on both days of the screening DBPCFC.
Demographics, medical history	Includes allergy history (including anaphylactic reactions) and symptoms, and diet/food allergen history.
Weight, height	
Vital signs	Measure blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation level.
Asthma evaluation	For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria (Table 16) before the DBPCFC on both days of the screening DBPCFC.
EASI score	For subject with eczema or atopic dermatitis. Assess eczema or atopic dermatitis.
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 parent/caregiver has an epinephrine auto-injector, including appropriate dose and expiry. Instruct that subject is to avoid peanut during the study. Document the discussion in the subject's source records.
Complete 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 that subject is to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction 5 half-lives of the medication before the screening skin prick test and DBPCFC, and first dose of dose escalation. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.
Skin prick test	Perform before the DBPCFC begins (same day or any previous day are acceptable). Measure mean wheal diameter and mean erythema diameter for peanut extract.

Activity	Comments
Laboratory Evaluations	Refer to the laboratory manual for sample collection and processing.
Hematology, immunology	Collect blood sample before the DBPCFC begins (same day or any previous day are acceptable). The total volume of blood collected is not to exceed 2 mL/kg per day (maximum 4 mL/kg in a 30-day period) or per local requirements. Complete blood count with differential. Total, peanut-specific, and peanut component-specific IgE. Peanut-specific and peanut component-specific IgG4.
Optional blood sample for evaluation of cellular responses to peanut antigen	At certain study sites only. Collect before the DBPCFC begins (same day or any previous day are acceptable).
DBPCFC and Eligibility Confirmation	
DBPCFC	Conduct on 2 separate days within 7 days. Measure vital signs and assess signs/symptoms of allergic reaction just before each challenge dose, and at least every 15-20 minutes postdose if the dosing interval between challenge dosing is prolonged. Refer to Appendix 1 for details.
Eligibility Confirmation	Confirm eligibility after completion of all screening activities.

DBPCFC, double-blind, placebo-controlled food challenge; EASI, Eczema Area and Severity Index; ID, identification; Ig, immunoglobulin; NHLBI, National Heart, Lung, and Blood Institute; TRACK, Test for Respiratory and Asthma Control in Kids.

Appendix 5: Study Schedule of Activities: Treatment (Initial Dose Escalation, Up-Dosing, and Maintenance)

Study Period	**Initial Dose Escalation**		**Up-Dosing**			**Maintenance**		**ED /**
Study Visit	**Day 1 [1]**	**Day 2 [2]**	**At Study Site**	**At 80 mg**	**At 300 mg**	**At Study Site**	**Unsch [3]**	**Exit [4]**
Interval	**na**	**na**	**q2w up to 40w**	**Varies**	**Varies**	**q4w × 12-24w [5]**	**Varies**	**Varies**
Window (Days)	**na**	**na**	**±3**	**±3**	**±3**	**±3**	**na**	**±5**
Randomization	X							
General Activities								
TRACK [6]				X	X	X	X (opt)	X [6]
Weight, height	X	X	X	X	X	X	X	X
Vital signs [7]	X	X	X	X	X	X	X	X
Asthma evaluation [8]				X	X	X	X (opt)	X [8]
EASI score [9]				X	X		X (opt)	X [10]
Symptom-directed physical examination [11]		X	X			X	X	
Complete physical examination [11]	X			X	X		X (opt)	X
Diet/food allergen exposure review	X	X	X	X	X	X	X	X
Food allergy instruction [12]	X	X	X	X	X	X	X (opt)	X
Adverse events review [13]	X	X	X	X	X	X	X	X
Concomitant medications review & instruction [14]	X	X	X	X	X	X	X	X
Study product administration [15]	X	X	X	X	X	X	X (opt)	
Study product dispensing [16]		X	X	X	X	X	X (opt)	
Study product accountability			X	X	X	X	X (opt)	X
Telephone call [17]		X	X	X	X	X	X (opt)	X
Skin prick test to peanut extract								X [10]
Palatability survey								X
DBPCFC [18]								X
Laboratory Evaluations [19]								
Hematology, immunology [20]								X [10]
Optional blood sample for evaluation of cellular responses to peanut antigen (certain study sites only)								X [10]

[1] Day 1 activities must begin within 42 days after obtaining signed consent and assent (where required) and within 10 days after the second day of the screening DBPCFC. The timing of day 1 study product administration, vital signs, and assessment of allergic reactions for initial dose escalation is presented in Table 2.

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

[3] Anytime necessary to assess or follow up adverse events, at the request of the parent/caregiver, or per investigator decision. Perform procedures as appropriate.

[4] Early discontinuation: For subject who discontinues treatment early; approximately 14 days after the last dose.
Exit: For subject who completes initial dose escalation, up-dosing, and maintenance for an overall total of approximately 12 months of treatment, and both days of the exit DBPCFC. If the follow-on study is not yet available at the study site, blinded study treatment may continue and the visit schedule will be every 4 weeks until the follow-on study is available.
For subject not enrolling in the follow-on study, the exit visit is approximately 14 days after the last dose.

[5] The first maintenance visit will occur after 300 mg/day is tolerated for 2 weeks during up-dosing. Maintenance treatment will continue daily for an overall total of approximately 12 months of treatment. The duration of maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks).

[6] For subject with asthma. Instruct parent/caregiver to complete TRACK at the start of the visit before other procedures and before the DBPCFC on both days of the DBPCFC.

[7] Vital signs include blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation level. Measure predose, at 15-30 minutes postdose, and every approximately 30 minutes thereafter (until at least 90 minutes postdose or end of observations for allergy symptoms, whichever is last). During maintenance treatment, the postdose observation period may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.

[8] For subject with asthma. Evaluate asthma severity per 2007 NHLBI criteria (Table 16). Evaluate asthma before the DBPCFC on both days of the DBPCFC.

[9] For subject with eczema or atopic dermatitis. Assess eczema or atopic dermatitis.

[10] Perform/collect at early discontinuation visit or before the exit DBPCFC begins (same day or any previous day within the exit visit window are acceptable).

[11] 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).

[12] Instruct that subject is 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.

[13] Include review of symptoms recorded in subject diary. For subject with GI adverse events of interest, instruct 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 exit and subject with GI adverse events of interest will have safety follow-up per Appendix 6.

[14] Review medications since previous visit. Instruct that subject is to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction 5 half-lives of the medication before initial dose-escalation day 1, skin prick tests, and the exit DBPCFC. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.

[15] Administer study product at the study site per the dose-escalation schedules and dose modification guidelines. Measure vital signs and assess signs/symptoms of allergic reaction at 15-30 minutes postdose and every approximately 30 minutes thereafter (until at least 90 minutes postdose or end of observations for allergy symptoms, whichever is last). During maintenance treatment, the postdose observation period may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.

[16] 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 days of the exit DBPCFC.

[17] Contact parent/caregiver by telephone for adverse events review and to inquire about compliance with study product dosing on the day after initial dose-escalation day 2, up-dosing visits, maintenance visits, and the exit DBPCFC. Remind parent/caregiver to record symptoms in the diary (except after completion of the exit DBPCFC).

[18] For subject who completes an overall total of approximately 12 months of treatment and tolerates the 300 mg daily dose of study product for at least 2 consecutive weeks before having the exit DBPCFC. Conduct on 2 separate days within 7 days.

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

[20] Complete blood count with differential. Total, peanut-specific, and peanut component-specific IgE. Peanut-specific and peanut component-specific IgG4.

DBPCFC, double-blind, placebo-controlled food challenge; EASI, Eczema Area and Severity Index; ED, early discontinuation; GI, gastrointestinal; Ig, immunoglobulin; na, not applicable; NHLBI, National Heart, Lung, and Blood Institute; opt, optional; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0; q, every; TRACK, Test for Respiratory and Asthma Control in Kids; unsch, unscheduled; w, weeks.

Appendix 6: Study Schedule of Activities: Safety Follow-Up

Activity	Ongoing Adverse Events at Early Disc / Exit [1]	GI Adverse Events of Interest	
		Dose Interruption > 7 Consecutive Days Due to GI AEs	Early Disc Due to GI AEs [2]
Adverse events review [3]	X		X
Concomitant medications review			X
Symptom-directed physical examination [4]			X
PEESS v2.0 questionnaire [5]		X	X

[1] Safety follow-up is for at least 30 days or until the adverse events resolve or stabilize (whichever is last), or until consent for follow-up is withdrawn.

[2] Safety follow-up at the study site or by telephone if appropriate. Includes review of medical records and procedure results from specialist visits (eg, endoscopy, pathology) if applicable, monthly for the duration of safety follow-up (Section 5.5.1).

[3] For adverse events ongoing at early discontinuation or study exit. Telephone parent/caregiver for subject who does not come to the study site.

[4] 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.

[5] Instruct parent/caregiver to complete the questionnaire at early discontinuation or study exit and monthly for the duration of safety follow-up (Section 5.5.1).

AE, adverse event; Early Disc, early discontinuation; GI, gastrointestinal; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0.