Aimmune Therapeutics

CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 2 Study of AR201 Oral Immunotherapy for Desensitization in Children, Adolescents, and Young Adults With Hen Egg Allergy
Protocol Identifier:	AIME01
Phase:	2
Investigational Product:	AR201
Sponsor:	Aimmune Therapeutics 8000 Marina Blvd, Suite 300 Brisbane, CA 94005 United States
Reference Number:	IND 18626
Sponsor Medical Monitor:	Kari Brown, MD, MS Telephone: +1 (919) 864-2607 Email: kbrown@aimmune.com
Original Protocol:	0.0 – 05 Nov 2018
Amendments	
Global:	1.0 – 26 Feb 2019
Global:	2.0 – 18 Dec 2019
Global:	3.0 – 28 May 2020

This study will be conducted according to the principles that have their origin in the Declaration of Helsinki, principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.

Confidentiality Statement

The information contained in this document and all information provided to you related to AR201 are the confidential and proprietary information of Aimmune Therapeutics ("Aimmune"; Aimmune Confidential Information) and except as may be required by federal, state, or local laws or regulations, may not be disclosed to others without prior written permission of Aimmune. However, the investigator may disclose such information to supervised individuals working on study AIME01, provided such individuals agree to be bound to maintain the confidentiality of such information.

SYNOPSIS

Title of Study: Phase 2 Study of AR201 Oral Immunotherapy for Desensitization in Children, Adolescents, and Young Adults With Hen Egg Allergy

Short Title: AR201 for Desensitization of Subjects With Hen Egg Allergy

Protocol Identifier: AIME01

Reference Number: IND 18626

Phase of Development: 2

Number of Subjects: Approximately 84

Study Centers: Approximately 30

Purpose of the Study: To determine the efficacy and safety of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy.

Study Objectives:

Primary:

- Efficacy of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy assessed by single highest tolerated dose of at least 1000 mg dried egg white protein in a double-blind, placebo-controlled food challenge (DBPCFC)

Secondary:

- Safety and tolerability of AR201
- Efficacy of AR201 assessed by single highest tolerated dose of dried egg white protein in a DBPCFC

Exploratory:

- Tolerance to baked egg at study exit in subjects who develop dose-limiting allergy symptoms to baked egg at screening
- Changes in immune parameters
- Changes in pre-existing comorbid atopic disease control (asthma, atopic dermatitis, allergic rhinitis)
- Changes in disease-specific measures of health-related quality of life

Study Design:

This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy. The study will be conducted at approximately 30 sites in the United States.

Eligible subjects who develop dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a screening DBPCFC will be randomly assigned 2:1 to blinded treatment with AR201 or placebo. Randomization will be stratified by baseline reactivity to baked egg in an open baked whole egg food challenge at screening. Subjects who tolerate approximately 2000 mg cumulative baked egg protein (one muffin which contains approximately one-third of one whole egg) will be allowed to consume baked egg products per Mount Sinai guidelines. Subjects who have dose-limiting symptoms during the open baked whole egg food challenge will be considered baked egg intolerant and will be instructed to avoid all forms of hen egg during the study.

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 5 single doses of 0.2, 0.4, 0.8, 1, and 2 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate at least the 1 mg single dose and have no more than mild or moderate symptoms at the 2 mg single dose on day 1 will return on day 2 for a single confirmatory 1 mg dose. Subjects who tolerate the confirmatory 1 mg dose with no more than mild symptoms that are not dose-limiting will begin the up-dosing period. Subjects who do not tolerate the 1 mg dose or who have severe symptoms at any dose during initial dose escalation will discontinue early from the study.

Up-dosing will be approximately 6 months (22-40 weeks), with dose escalation occurring 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 reach the 300 mg/day dose within 40 weeks and tolerate the first 300 mg dose with no more than mild symptoms that are not dose-limiting will begin the maintenance period. Subjects who do not reach the 300 mg/day dose within 40 weeks of day 1 will discontinue early from the study.

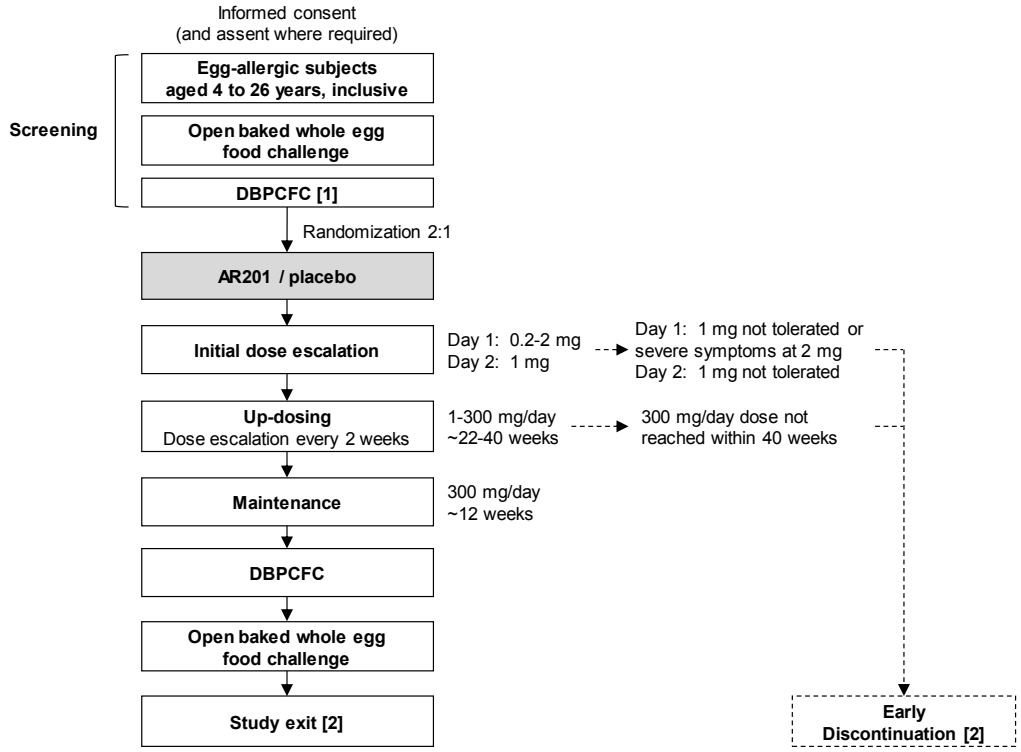
Subjects who begin maintenance treatment will continue daily dosing with study product at 300 mg/day for approximately 12 weeks, which may be extended by up to an additional 4 weeks to accommodate dose adjustments during the last 2 weeks of maintenance. Study site visits will occur approximately every 4 weeks. Study product will be administered under medical supervision at the study site during maintenance visits; subsequent maintenance doses will be administered daily at home as tolerated. At the end of maintenance, subjects will have an exit DBPCFC up to a single highest challenge dose of 2000 mg dried egg white protein (4043 mg cumulative) or placebo, followed by an open baked whole egg food challenge within 14 days after the second day of the exit DBPCFC. Subjects must tolerate the 300 mg daily dose of study product for approximately 2 consecutive weeks before having the exit DBPCFC.

Subjects who complete the exit DBPCFC and attempt the open baked whole egg food challenge will exit (complete) the study. Study treatment assignment will be unblinded for a subject after study exit and after all major data queries for the subject are resolved. For a subject who discontinues early from the study, study treatment assignment will be unblinded after the study is completed. Eligible subjects will have the option to enroll in an open-label, follow-on study to receive AR201 treatment until it becomes commercially available or product development is terminated.

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, beginning 6 months after the first subject is enrolled in the study.

Study Schematic:



[1] Eligible subjects must have dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a 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 4 to 26 years, inclusive, at randomization; have a history of physician-diagnosed immunoglobulin E (IgE)-mediated hen egg allergy; serum IgE to egg white of ≥ 5 kUA/L and/or a mean wheal diameter on skin prick test to egg white of at least 5 mm greater than the negative control (saline) at screening; and have dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a screening DBPCFC. Written informed consent and assent (as appropriate) is required. Subjects must not have a history of severe or life-threatening anaphylaxis within 60 days before screening; history of non-IgE-mediated hen egg allergy (eg, food protein-induced enterocolitis syndrome [FPIES]); history of eosinophilic esophagitis (EoE) or other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); symptoms of dysphagia; recurrent GI symptoms of unknown etiology; history of a mast cell disorder (eg, systemic mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism [eg, cold urticaria, cholinergic urticaria], or hereditary or idiopathic angioedema); have mild or moderate asthma that is uncontrolled or difficult to control or severe persistent asthma; history of high-dose corticosteroid medication use (eg, > 3 days at 1-2 mg/kg of prednisone or equivalent); or history of cardiovascular disease (including uncontrolled or inadequately controlled hypertension).

Test Product, Dose, and Mode of Administration:

AR201 consists of dried egg white formulated with diluents and flow agents in graduated doses. AR201 will be provided in pull-apart hypromellose capsules containing 0.2, 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, or 300 mg egg white protein. Capsules will be opened; the contents delivered over an age-appropriate, semisolid, vehicle food; and mixed thoroughly before administration.

The sponsor will supply the AR201 for this study.

Reference Therapy, Dose, and Mode of Administration:

Placebo is formulated with the inactive ingredients used in AR201, and without dried egg white. Placebo contains inactive ingredients to match the color and texture of dried egg white, and will be provided as capsules identical to the AR201 test product capsules. Capsules will be opened; the contents delivered over an age-appropriate, semisolid, vehicle food; and mixed thoroughly before administration.

The sponsor will supply the placebo to match AR201 for this study.

Duration of Treatment:

The total duration of treatment is approximately 9 months for each subject.

The total duration of the study is approximately 22 months.

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.

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 one dose of study product. Randomization will be central and treatment allocation will be 2:1 to AR201 or placebo. Randomization will be stratified by baseline reactivity (tolerant or intolerant) to baked egg in an open baked whole egg food challenge at screening. Subjects who tolerate approximately 2000 mg cumulative baked egg protein without dose-limiting allergy symptoms will be considered baked egg tolerant. Subjects who do not complete the screening open baked whole egg food challenge for reasons other than dose-limiting symptoms and who have a clear clinical history of tolerance to baked egg may be considered baked egg tolerant after discussion with the medical monitor. All other subjects will be considered baked egg intolerant.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of subjects treated with AR201 compared with placebo who tolerate a single highest dose of at least 1000 mg dried egg white protein with no more than mild allergy symptoms at the exit DBPCFC.

Secondary Efficacy Endpoint:

- Proportion of subjects who tolerate a single highest dose of at least 300 mg dried egg white protein with no more than mild symptoms during the exit DBPCFC
- Proportion of subjects who tolerate a single highest dose of at least 600 mg dried egg white protein with no more than mild symptoms during the exit DBPCFC
- The maximum severity of allergy symptoms after consuming dried egg white 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 AR201 treatment in a follow-on study. 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 systemic allergic reaction grading system for systemic allergic reactions including anaphylaxis, and the general adverse event grading system for all other adverse events. Anaphylaxis is defined as a severe, potentially life-threatening systemic allergic reaction (ie, grade ≥ 3 per the systemic allergic reaction grading system) that meets the protocol-specified criteria for anaphylaxis.

The safety of AR201 treatment versus placebo will be evaluated by analyzing 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 adverse events considered allergic reactions, systemic allergic reactions, use of epinephrine, and accidental and nonaccidental food allergen exposure. Summary statistics will be provided for the Asthma Control Test

(ACT), Childhood Asthma Control Test (C-ACT), lung function data, Eczema Area and Severity Index (EASI), Total Nasal Symptom Score (TNSS), and laboratory data if relevant.

Exploratory Endpoints:

Exploratory endpoints will be assessed as follows:

- Proportion of subjects who develop dose-limiting symptoms to approximately 2000 mg cumulative baked egg protein at screening and subsequently tolerate approximately 2000 mg cumulative baked egg protein with no more than mild symptoms at study exit
- Proportion of subjects who tolerate a single highest dose of 2000 mg dried egg white protein with no more than mild symptoms at the exit DBPCFC
- Maximum dose of dried egg white protein reached with no more than mild symptoms during the exit DBPCFC
- Change from baseline in the single highest tolerated dose of dried egg white protein at the exit DBPCFC
- Use of epinephrine as rescue medication at the exit DBPCFC compared with use at the screening DBPCFC
- Change from baseline in egg white-specific and egg white component serum immunoglobulins
- Change from baseline in mean wheal diameter on skin prick test to egg white
- Change from baseline in ACT/C-ACT, EASI, and TNSS scores
- Change from baseline in Food Allergy Quality of Life (FAQLQ) and Food Allergy Independent Measure (FAIM) scores

Sample Size Considerations:

A sample size of 84 subjects randomly assigned at a ratio of 2:1 to AR201 or placebo (56 AR201, 28 placebo) provides 89% power to demonstrate a significant treatment difference of at least 35% in desensitization response rate with AR201 compared with placebo for the primary efficacy endpoint of the proportion of subjects tolerating an at least 1000 mg single dose of dried egg white protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on a 2-sided alpha of 0.05, and 2-sample comparison of binomial proportions with an assumed maximum desensitization rate of 60% in the AR201 group and 25% in the placebo group. Treated subjects who discontinue early from the study 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) and 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
ACT	Asthma Control Test
C-ACT	Childhood Asthma Control Test
CFR	Code of Federal Regulations
DBPCFC	Double-blind, placebo-controlled food challenge
DSMC	Data and safety monitoring committee
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
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FEV_1	Forced expiratory volume in the first second of expiration
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
NHLBI	National Heart, Lung, and Blood Institute
OIT	Oral immunotherapy
PEESS v2.0	Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0
PEF	Peak expiratory flow
SPT	Skin prick test
SUSAR	Suspected unexpected serious adverse reaction
TNSS	Total Nasal Symptom Score
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Background

Hen egg allergy is a common and serious condition that disproportionately affects children and is associated with severe hypersensitivity reactions, including life-threatening anaphylaxis. The prevalence of egg allergy is estimated to be approximately 0.5% to 2.5% in Western countries (Loh, 2018). While egg allergy is typically outgrown, longitudinal studies have shown this may not occur until the second decade of life, with egg allergy persisting in approximately 20% of individuals aged 18 years (Clark, 2011; Savage, 2007). Higher peak egg-specific immunoglobulin E (IgE) levels, higher initial egg-specific IgE, and initial allergic reaction characteristics have been suggested to be predictive of persistence of egg allergy into adulthood (Sicherer, 2014; Lemon-Mule, 2008; Savage, 2007).

Two main egg allergy phenotypes are recognized in the clinic, allergy to both raw egg and baked egg, and allergy to raw egg only (Bartnikas, 2013; Tan, 2013; Turner, 2013; Lieberman, 2012; Osborne, 2011; Lemon-Mule, 2008). Approximately 20% to 30% of individuals with egg allergy are allergic to both raw egg and baked egg, and 70% to 80% of individuals with egg allergy are allergic to raw egg only (Tan, 2013; Turner, 2013; Lieberman, 2012; Osborne, 2011; Lemon-Mule, 2008). Allergy to well-cooked egg (baked egg) has been shown to resolve at a more rapid rate than allergy to uncooked egg (raw egg) (Clark, 2011).

The current standard of care for the management of egg allergy is dietary avoidance of egg and education of the patient/family on recognition and management of allergy symptoms and appropriate use of rescue medications (eg, epinephrine auto-injectors). Regular consumption of baked egg by patients with hen egg allergy who tolerate baked egg has been proposed to accelerate the development of tolerance to raw egg compared with avoidance (Leonard, 2012). However, it is not known whether the decreased time to resolution of hen egg allergy is due to regular consumption of baked egg by patients allergic to raw egg only or if these patients represent an egg allergy phenotype with a greater probability of outgrowing the egg allergy (Lambert, 2017; Dang, 2014).

Avoidance of egg is exceptionally difficult for patients with egg allergy because of the ubiquity of egg as an ingredient in many food products. 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. Thus, accidental exposure to egg is common; accidental exposure remains a major concern because allergic responses may be triggered by minute quantities (milligrams) of egg protein (Zhu, 2015; Blom, 2013; Eller, 2012). A recent observational study showed that after a median follow-up of 3 years, allergic reactions to egg accounted for 21% of allergic reactions to a food allergen, with an annualized rate of allergic reactions to egg of 0.17 (95% CI: 0.15, 0.19); 729 of 834 (87.4%) reactions to milk, egg, or peanut were due to accidental exposures (Fleischer, 2012). The burden of avoidance and constant fear of accidental exposure can negatively affect the

health-related quality of life of individuals with egg allergy and their families (Howe, 2014; Lieberman, 2011). Additionally, daily carriage and emergency use of epinephrine auto-injectors for the treatment of anaphylaxis are thought to be inadequate, which can lead to adverse outcomes including hospitalization and death (Warren, 2018).

There are no approved interventional therapies for egg allergy, and current therapies are designed to only treat the symptoms of allergic reactions. Thus, in the absence of a cure, therapies with the potential to reduce the risk of severe allergic reaction in the event of an accidental exposure represent an urgent unmet medical need.

Oral immunotherapy (OIT) for egg allergy has been widely studied in recent years and has demonstrated encouraging safety and efficacy results in clinical studies (Feuille, 2018; Yee, 2016; Ibanez, 2015). However, the studies were heterogenous with respect to key variables such as the form of study product, dosing scheme, primary and secondary endpoints, and safety data collection. The form of study product used for desensitization has included dried egg white (also called dehydrated egg white), dry powdered egg, raw egg, liquid egg white, scrambled egg, and hydrolyzed egg. Study product used for maintenance dosing and dose levels have varied, with studies using as low as 300 mg dried egg white daily and others utilizing one whole egg daily (equivalent to approximately 3.6 g egg white protein). Despite the heterogeneity of clinical study protocols, egg forms, maintenance doses, and dose thresholds in the exit oral food challenge assessment, favorable desensitization responses were reported across studies using nonhydrolyzed egg study material for OIT (Feuille, 2018; Romantsik, 2018; Graham, 2017; Yee, 2016). In a recent systematic review of 10 randomized controlled studies that included egg OIT, a control group (placebo or egg avoidance diet), and patients aged 1 to 18 years, 82% of the 249 subjects in the egg OIT group compared with 10% of the 190 subjects in the control group could ingest a partial serving of egg (1-7.5 g egg protein), resulting in a pooled risk ratio of 7.48 (95% CI: 4.91, 11.38) (Romantsik, 2018).

The largest egg OIT study conducted in the United States to date was a randomized, double-blind, placebo-controlled, multicenter study of dried egg white OIT in 55 children aged 5 to 11 years with egg allergy (40 egg OIT, 15 placebo) (Burks, 2012). Subjects were enrolled based on suggestive or diagnostic baseline clinical characteristics. Study sites included 5 leading food allergy centers of the National Institutes of Health-supported Consortium of Food Allergy Research (CoFAR). Initial dose escalation, up-dosing, and maintenance with up to 2 g/day egg white powder (approximately 1.6 g egg white protein or one-third of an egg) were followed by food challenges with 5 g egg white powder at 10 months and 10 g egg white powder at 22 months. After 10 months of study treatment, 22 of 40 egg OIT-treated subjects (55%) and 0 of 15 placebo-treated subjects passed the food challenge (ie, tolerated 5 g egg white powder with no clinically significant allergy symptoms). At 22 months, 30 of 40 egg OIT-treated subjects (75%) tolerated 10 g egg white powder in the food challenge with no clinically significant allergy symptoms.

Adverse event rates reported in published egg OIT studies have been variable due to the heterogeneity of egg OIT dosing protocols, baseline egg sensitivity of the study populations, and safety reporting methods. Additionally, the frequency and severity of adverse events were not consistently reported by treatment period (ie, initial dose escalation, up-dosing, and

maintenance) across studies, with few studies reporting adverse events during the maintenance period (Ibanez, 2015). During egg OIT, most subjects experience adverse events, the majority of which are mild to moderate; in 2 studies of OIT using dried egg white, moderate adverse events were far less frequent during maintenance compared with up-dosing (Ibanez, 2015). In the systematic review by Romantsik et al, 75% of egg OIT-treated subjects experienced mild to severe adverse events compared with 6.8% of placebo-treated subjects, with most adverse events occurring during dose escalation in association with OIT dosing (Romantsik, 2018). In the CoFAR study, adverse events were associated with 25.0% of OIT doses and 3.9% of placebo doses during the first 10 months of treatment (which included initial dose escalation [1 day], build-up [32-40 weeks], and maintenance [approximately 8 weeks]) (Burks, 2012). Less than 1% of OIT and placebo doses were associated with moderate adverse events, and no serious adverse events related to dosing were reported. After 10 months of treatment, the overall adverse event rate decreased, with 8.3% of egg OIT doses associated with adverse events. The most frequently reported adverse events included oral or pharyngeal (15.4% of OIT doses and 0.2% of placebo doses), respiratory (7.8% and 2.4%), gastrointestinal (5.5% and 0.3%), and skin (4.4% and 0.8%). Seven subjects (13%) withdrew before the maintenance phase, 2 receiving placebo and 5 receiving OIT. Long-term follow-up showed that adverse events were less frequent and limited to mild severity with continued egg OIT (Jones, 2016). Of 22 subjects who continued OIT after year 2, the median percentage of doses per subject associated with adverse events was 8.0% before year 2 and 0.2% after year 2. The results of these studies and other experience with OIT in other common food allergies (Beyer, 2012; Keet, 2012) provide the rationale for initial clinical development of AR201 for patients with hen egg allergy.

AR201 consists of dried egg white formulated with diluents and flow agents in graduated doses. The goal of continuous treatment with AR201 is to induce and maintain a state of clinically meaningful desensitization to egg white protein, defined as no more than mild allergy symptoms following ingestion of small but potentially dangerous amounts of egg white protein by patients with egg allergy. This state of desensitization is hypothesized to be sufficient to protect a patient with egg allergy from severe allergic reactions following accidental exposure to egg despite maintaining an egg avoidant diet. Although threshold exposure levels for allergic reactions vary within the population with egg allergy, the dose predicted to elicit an allergic reaction in 10% of patients with egg allergy is low, ranging from 3.7 mg to 5.8 mg egg protein (Zhu, 2015; Blom, 2013; Eller, 2012).
Four well-documented events of known accidental egg exposure in 2 patients showed that maintenance therapy at doses of 200 and 300 mg egg protein provided a clinically meaningful level of desensitization to egg. In the patient receiving maintenance therapy at a dose of 200 mg egg protein, no clinical symptoms of an allergic reaction were observed following accidental ingestion of an egg-containing cake (approximately 50 mg egg protein) (Buchanan, 2007). In the patient receiving maintenance therapy at a dose of 300 mg egg protein, no clinical symptoms of an allergic reaction were observed following accidental ingestion of an egg-containing cupcake (approximately 600 mg egg protein), 1 bite of an egg-containing cake (approximately 50 mg egg protein), and an egg-containing cookie (approximately 300 mg egg protein) (Buchanan, 2007). Accordingly, desensitization to at least 300 mg dried egg white is expected to provide a clinically meaningful level of protection against most accidental exposures to egg.

1.2 Summary of Relevant Clinical Experience With AR201

This is a first-in-human study of AR201.

1.3 Summary of Relevant Nonclinical Experience With AR201

AR201 has not been tested in animals.

1.4 AR201 Benefits and Risks Assessment

Egg is a common food and is not associated with side effects when consumed in a normal diet, except for allergic reactions in patients with egg allergy.

Initial dosing with low doses of AR201, followed by up-dosing with the first dose at each new dose level administered under medical supervision, is expected to reduce the likelihood of a subject experiencing a severe allergic reaction. Additionally, subjects will be required to have an epinephrine auto-injector; subjects and parents/caregivers will be instructed on recognition and management of allergy symptoms and appropriate use of rescue medications, including epinephrine auto-injectors. To decrease the potential risks to subjects, study sites with experience with OIT in pediatric subjects will be chosen for this study. Stopping rules will be applied if prespecified study suspension criteria are met. Additionally, an independent data and safety monitoring committee (DSMC) will review safety data on an ongoing basis.

The most common risk associated with AR201 administered to subjects with egg allergy is expected to be allergy symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing, and/or shortness of breath in addition to anaphylaxis. The allergy symptoms are expected to be mostly mild and self-limited. Results from previous egg OIT studies showed that the vast majority of symptoms were mild and consistent with stimulation of a transient, low-grade allergic reaction. Across the clinical studies, symptoms tended to diminish with increasing treatment duration.

There are no approved treatments for egg allergy despite advances in understanding the causes of food allergy, strategies for food allergy prevention, and the mechanisms underlying tolerance. Available therapies are designed to treat only the symptoms of allergic reactions when they occur. Thus, in the absence of a cure, therapies with the potential to reduce the risk of severe allergic reaction in the event of an accidental exposure are an urgent unmet need. Allergen-specific immunotherapy is an approach that has shown consistent and promising results. Several clinical studies have demonstrated promising efficacy and safety profiles of egg OIT, supporting this therapeutic approach in patients with egg allergy. However, the heterogeneity and relatively small sample sizes of previous clinical studies point to the need for a blinded, randomized, placebo-controlled clinical study with phenotypic characterization of the study population, systematic safety reporting, and utilization of a drug product that has been manufactured according to Good Manufacturing Practices.

1.5 Purpose of the Study

The purpose of this study is to determine the efficacy and safety of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy.

1.6 Rationale for Study Design

Egg OIT has been widely studied in recent years but the studies varied significantly in study design. Despite the differences between protocols, all studies utilizing nonhydrolyzed egg products showed favorable desensitization responses with egg OIT and an expected safety profile comprised of mainly mild to moderate allergic adverse events (Romantsik, 2018). These data support the initiation of a phase 2 clinical study for AR201.

Subjects up to 26 years of age will be enrolled due to the high unmet medical need in this population, indicated by the increased risk of fatal food-induced anaphylaxis in adolescents and young adults (Bock, 2001). Given the natural history of spontaneous resolution, adults aged 26 years or older will not be enrolled in this study. A lower age limit of 4 years was selected based on the known spontaneous resolution rate of egg allergy, which is the greatest in younger children (Sicherer, 2014).

Randomization will be stratified by baseline tolerance or reactivity to baked whole egg, as baked egg tolerance is a known predictor for spontaneous resolution of egg allergy (Leonard, 2015).

A standardized method for OIT with AR201 will be used that consists of initial dose escalation at low doses, gradual up-dosing over time to limit allergic reactions (single dose escalation every 2 weeks), and maintenance dosing at 300 mg/day dried egg white protein. The aim of treatment with AR201 is to induce and maintain a state of desensitization to egg that is sufficient to protect a patient with egg allergy from severe symptoms in case of accidental exposure despite maintaining an egg-avoidant diet. Therefore, the maintenance dose is lower than that used in clinical studies whose aim was to achieve nutritional inclusion of egg in the diet. The AR201 dosing regimen is based in part on that used by Buchanan et al, where 24 months of maintenance treatment with 300 mg egg OIT resulted in 6 of 7 subjects (85.7%) tolerating > 2 g egg white powder in an exit oral food challenge, an amount that is 6-fold greater than the maintenance dose (Buchanan, 2007).

Study AIME01 is designed to assess the initial efficacy and safety of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy. The primary efficacy endpoint is the proportion of subjects tolerating a single highest dose of at least 1000 mg dried egg white protein with no more than mild symptoms at the exit double-blind, placebo-controlled food challenge (DBPCFC). The DBPCFC will be performed according to Practical Allergy (PRACTALL) guidelines (Sampson, 2012), with modification to include single challenge doses of 600 mg and 2000 mg. Based on the literature, tolerance of 1000 mg dried egg white protein would offer clinically relevant protection against typical accidental exposures to egg while on an avoidance diet. Data from published studies have estimated the eliciting dose for an allergic reaction in 50% of patients with egg allergy to be approximately 199 mg of protein (Blom, 2013). Accidental exposures to egg are more likely to occur with food in

which egg is not the main ingredient (ie, glazes, sauces, dressings). The amount of egg white protein that would be ingested from exposure to these foods is considerably less than the amount of egg white protein in one egg (approximately 3.6 g). Although systematic studies investigating the amount of egg white protein in accidental exposures have not been performed, the estimated amount of egg protein in accidental exposures while undergoing egg OIT was reported to range from 50 to 600 mg (Buchanan, 2007). These data suggest desensitization to 1000 mg dried egg white protein is appropriate to assess for desensitization to a clinically relevant amount of egg.

2 STUDY OBJECTIVES

2.1 Primary Objective

- Efficacy of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy assessed by single highest tolerated dose of at least 1000 mg dried egg white protein in a DBPCFC

2.2 Secondary Objectives

- Safety and tolerability of AR201
- Efficacy of AR201 assessed by single highest tolerated dose of dried egg white protein in a DBPCFC

2.3 Exploratory Objectives

- Tolerance to baked egg at study exit in subjects who develop dose-limiting allergy symptoms to baked egg at screening
- Changes in immune parameters
- Changes in pre-existing comorbid atopic disease control (asthma, atopic dermatitis, allergic rhinitis)
- Changes in disease-specific measures of health-related quality of life

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This is a phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR201 in subjects aged 4 to 26 years, inclusive, with hen egg allergy. The study will be conducted at approximately 30 sites in the United States.

Eligible subjects who develop dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a screening DBPCFC will be randomly assigned 2:1 to blinded treatment with AR201 or placebo. Randomization will be stratified by baseline reactivity to baked egg in an open baked whole egg food challenge at screening. Subjects who tolerate approximately 2000 mg cumulative baked egg protein (one muffin which contains approximately one-third of one whole egg) will be allowed to consume baked

egg products per Mount Sinai guidelines (Lieberman, 2012). Subjects who have dose-limiting symptoms during the open baked whole egg food challenge will be considered baked egg intolerant and will be instructed to avoid all forms of hen egg during the study.

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 5 single doses of 0.2, 0.4, 0.8, 1, and 2 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate at least the 1 mg single dose on day 1 and have no more than mild or moderate symptoms at the 2 mg single dose will return on day 2 for a single confirmatory 1 mg dose. Subjects who tolerate the confirmatory 1 mg dose with no more than mild symptoms that are not dose-limiting will begin the up-dosing period. Subjects who do not tolerate the 1 mg dose or who have severe symptoms at any dose during initial dose escalation will discontinue early from the study.

Up-dosing will be approximately 6 months (22-40 weeks), with dose escalation occurring 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 reach the 300 mg/day dose within 40 weeks and tolerate the first 300 mg dose with no more than mild symptoms that are not dose-limiting will begin the maintenance period. Subjects who do not reach the 300 mg/day dose within 40 weeks of day 1 will discontinue early from the study.

Subjects who begin maintenance treatment will continue daily dosing with study product at 300 mg/day for approximately 12 weeks, which may be extended by up to an additional 4 weeks to accommodate dose adjustments during the last 2 weeks of maintenance. Study site visits will occur approximately every 4 weeks. Study product will be administered under medical supervision at the study site during maintenance visits; subsequent maintenance doses will be administered daily at home as tolerated. At the end of maintenance, subjects will have an exit DBPCFC up to a single highest challenge dose of 2000 mg dried egg white protein (4043 mg cumulative) or placebo, followed by an open baked whole egg food challenge within 14 days after the second day of the exit DBPCFC. Subjects must tolerate the 300 mg daily dose of study product for approximately 2 consecutive weeks before having the exit DBPCFC.

Subjects who complete the exit DBPCFC and attempt the open baked whole egg food challenge will exit (complete) the study. Study treatment assignment will be unblinded for a subject after study exit and after all major data queries for the subject are resolved. For a subject who discontinues early from the study, study treatment assignment will be unblinded after the study is completed. Eligible subjects will have the option to enroll in an open-label, follow-on study to receive AR201 treatment until it becomes commercially available or product development is terminated.

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 per Section 5.5. Safety follow-up procedures are listed in Appendix 6.

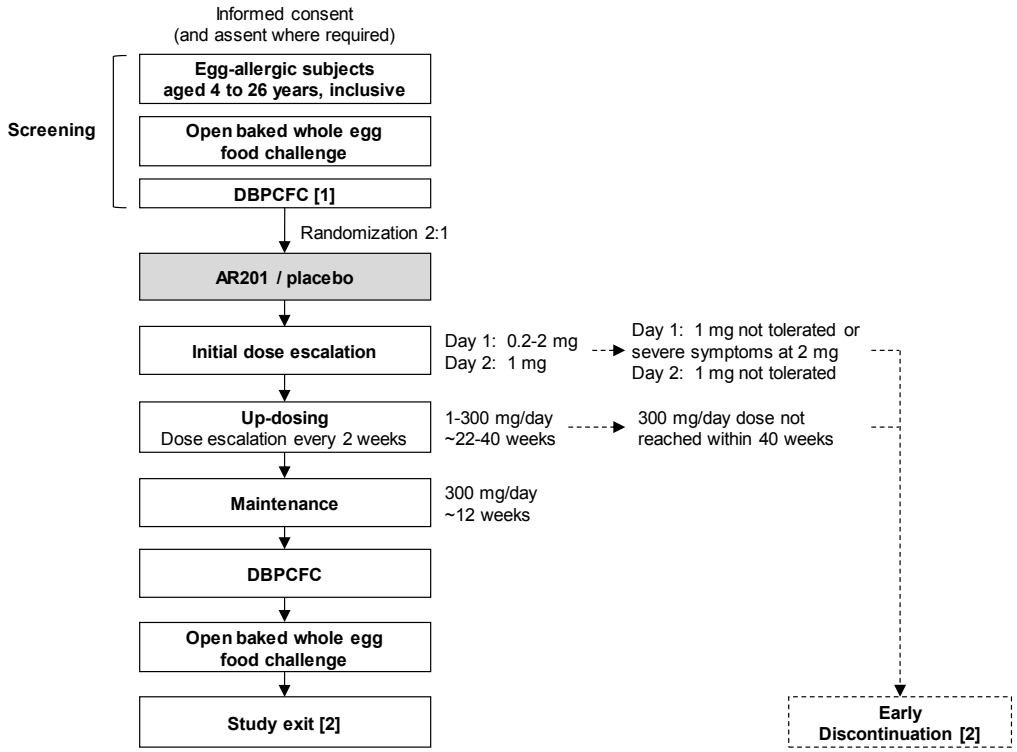
An independent, external DSMC will monitor safety on a periodic basis, beginning 6 months after the first subject is enrolled in the study.

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) and 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 dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a 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 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 egg and placebo challenge days, and prepare the DBPCFC material.

Subjects who complete the exit DBPCFC and attempt the open baked whole egg food challenge will exit (complete) the study; study treatment assignment will be unblinded after all major data queries for the subject are resolved. For a subject who discontinues early from the study, study treatment assignment will be unblinded after the study is completed.

3.4 Study Suspension Criteria

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

- A treatment-associated death in a subject receiving AR201
- Two subjects hospitalized within 6 months of each other for ongoing intensive treatment due to AR201-related adverse events
- Three subjects hospitalized for ongoing intensive treatment due to AR201-related adverse event
- Greater than 2 cases of AR201-related anaphylaxis resulting in hypotension, neurologic compromise, or mechanical ventilation (systemic allergic reaction grading system grade ≥ 3 per Section 8.6; clinical assessment per Section 8.4.1)

Admission to the hospital for observation only (not for ongoing intensive treatment of a serious AR201-related adverse event) will not be considered contributory to the study suspension criteria. Contributory events of anaphylaxis must be documented (including signs and symptoms and a clinical assessment) and meet the protocol-specified criteria for anaphylaxis. The DSMC may also recommend stopping the study for any substantial imbalance in adverse events apart from anticipated dosing-related allergy symptoms, based on their 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 regulatory authorities. 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 9 months for each subject.

The total duration of the study is approximately 22 months.

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 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 4 to 26 years, inclusive, at randomization.
2. Written informed consent from subjects, as appropriate per local requirements, and legal guardian/parent (or both parents where required by local authorities) of subjects who are minors.
3. Written assent from subjects who are minors, as appropriate per local requirements.
4. History of physician-diagnosed IgE-mediated hen egg allergy.
5. Serum IgE to egg white of ≥ 5 kUA/L and/or a mean wheal diameter on skin prick test (SPT) to egg white of at least 5 mm greater than the negative control (saline) at screening.
6. Development of dose-limiting allergy symptoms after consuming single doses of ≤ 300 mg dried egg white protein in a screening DBPCFC.
7. For sexually active females of childbearing potential, use of a highly effective method of birth control, defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly, as follows:
   - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
   - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner
   - Sexual abstinence

   If a highly effective single method of birth control is not used, an effective double-barrier method of contraception should be used (eg, male condom in conjunction with a cervical cap, diaphragm, or contraceptive sponge with spermicide).

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 within 60 days before screening.

2. History of non-IgE-mediated hen egg allergy such as food protein-induced enterocolitis syndrome (FPIES).
3. History of eosinophilic esophagitis (EoE); other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"); or recurrent GI symptoms of unknown etiology.
4. History of a mast cell disorder including systemic mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema.
5. Severe persistent asthma (criteria step 5 or 6; National Heart, Lung, and Blood Institute [NHLBI], 2007).
6. Mild or moderate asthma (criteria steps 1-4; NHLBI, 2007) that is uncontrolled or difficult to control as defined by any of the following:
   - Forced expiratory volume in the first second of expiration (FEV_1) < 80% of predicted, with or without controller medications (aged ≥ 6 years only and able to do spirometry)
   - Inhaled corticosteroid dosing of > 500 µg daily fluticasone (or equivalent based on NHLBI 2007 dosing chart)
   - Two or more asthma exacerbations requiring systemic corticosteroids within 1 year before screening
   - One hospitalization due to asthma within 1 year before screening
7. History of high-dose corticosteroid medication use (eg, > 3 days at 1-2 mg/kg of prednisone or equivalent) as defined by any of the following:
   - Oral steroid administered daily for > 1 month within 1 year before screening
   - Burst steroid course (oral, IV, or intramuscular administration) within 3 months before screening
   - More than 2 burst steroid courses (oral, IV, or intramuscular administration) ≥ 1 week in duration within 1 year before screening
8. History of chronic disease (except asthma, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in a chronic therapeutic regimen, including malignancies within 5 years before screening and autoimmune diseases.
9. History of cardiovascular disease including uncontrolled or inadequately controlled hypertension.
10. Use of beta-blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or tricyclic antidepressants.
11. Unable to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction for 5 half-lives of the medication before an SPT, food challenge, and the first day of dose escalation.
12. Lack of an available palatable vehicle food to which the subject is not allergic.
13. Development of dose-limiting symptoms to placebo challenge during the screening DBPCFC.

14. Hypersensitivity to wheat, oat, or any ingredient (except hen egg) in the food challenge materials.
15. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector.
16. Use of any therapeutic antibody or any immunomodulatory therapy (including immunosuppressive medications) within 6 months before screening, except aeroallergen or venom immunotherapy used in the maintenance phase.
17. Currently receiving or received within 5 years before screening any type of egg or other food allergen immunotherapy.
18. Participated in another interventional clinical study within 30 days or 5 half-lives of the investigational product, whichever is longer, before screening.
19. In the build-up phase of immunotherapy for any nonegg allergen.
20. Resides at the same place as another subject in any interventional trial sponsored by Aimmune.
21. Lives in the same household and/or is a family member of a sponsor employee or site staff involved in conducting this study.
22. Pregnant or breastfeeding.
23. Any other condition (concurrent disease, infection, comorbidity, or psychiatric or psychological disorders) or reason that may interfere with the ability to participate in the study, cause undue risk, or complicate the interpretation of data, in the opinion of the investigator or medical monitor.

5 ENROLLMENT AND STUDY PROCEDURES

Enrollment and general study procedures are summarized in the following subsections. The study periods will include screening and treatment. The treatment period for subjects receiving 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 potential study participants or 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.

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 discussion with the medical monitor.

5.2 Treatment Periods

5.2.1 Treatment Period Visit Windows

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 begin within 42 days after obtaining signed consent/assent and within 10 days after the second day of the screening DBPCFC. If circumstances create a safety risk (eg, an intercurrent illness), day 1 may be delayed after discussion with the medical monitor.

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 after discussion with the medical monitor.

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 (AR201 or placebo), which is to begin within 42 days after signed consent/assent and should be the same day as randomization. Randomized study treatment may start within 3 days after randomization only if starting the same day is not feasible (eg, for certain unexpected circumstances that may create a safety risk, such as intercurrent illness). A longer window may be allowed on a case-by-case basis following approval from the medical monitor.

5.2.3 General Study Visit Procedures

Day 1 will be the first day of randomized study treatment (AR201 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 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. Subjects will be evaluated for signs and symptoms of an allergic reaction at 15 to 30 minutes postdose and approximately every 30 minutes thereafter (with measurements of blood pressure and heart rate), until at least 90 minutes postdose or the end of the observation period (Section 8.7.1), whichever is last.

Allergy symptoms will be assessed as follows:

- Symptoms of allergic reactions will be evaluated per Section 8.7.1.
- The tolerability of study product will be evaluated per Section 8.7.1.1.
- The treatment of allergic reactions and dose adjustment of study product will follow guidelines per Section 8.7.2 and Section 8.7.3.

On the day after each study site visit, site staff will contact the subject or 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 subject or 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 5 increasing doses in a stepwise manner in 20- to 30-minute intervals as tolerated. The 5 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	0.2	0.2
2	0.4	0.6
3	0.8	1.4
4	1	2.4
5	2	4.4

The time points for study product dosing and assessments of blood pressure, heart rate, temperature, and allergic reaction are provided in Table 2. Subjects who develop dose-limiting or moderate allergy symptoms at ≤ 1 mg doses of study product, severe symptoms at any dose, or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.7.3.1) at ≤ 1 mg doses of study product or for severe symptoms at the 2 mg dose 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	Blood Pressure	Heart Rate	Temp	Assess Allergy Symptoms
Predose		X	X	X	
0.2 mg	X				
15-30 min postdose		X	X		X
0.4 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
0.8 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
1.0 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
2 mg (20-30 min after previous dose) [1]	X				
15-30 min postdose		X	X		X
Approximately every 30 min until at least 90 min after last dose or end of observation per allergy symptoms [2]		X	X		X

[1] If the previous dose was tolerated (Section 8.7.1.1). If the subject has dose-limiting or moderate allergy symptoms anytime at ≤ 1 mg, severe symptoms at any dose, or requires rescue medications (except ≤ 2 doses of antihistamines, Section 8.7.3.1) at ≤ 1 mg or for severe symptoms at 2 mg, stop dose escalation and discontinue the subject early from the study. If 1 mg is tolerated or no more than mild or moderate symptoms occur at 2 mg, the subject will return for a single 1 mg dose on day 2.

[2] The length of observation is based on signs/symptoms of allergic reaction per Section 8.7.1.

Min, minutes; temp, temperature.

Day 2

Subjects who tolerate at least 1 mg study product and have no more than mild or moderate allergy symptoms at the 2 mg dose 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 after discussion with the medical monitor. Subjects who tolerate the 1 mg dose with no more than mild 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 develop moderate or severe symptoms after consuming the 1 mg dose on day 2, or use rescue medications (except ≤ 2 doses of antihistamines, Section 8.7.3.1), 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. Additional procedures will be performed at the 80 mg and 300 mg up-dosing visits (Appendix 5).

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

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. AR201 dose escalations will continue in this manner up to 300 mg/day as shown in Table 3. Dose adjustments may be allowed (Section 8.7.3.2, Section 8.7.4).

Subjects who reach the 300 mg/day dose within 40 weeks and tolerate the first 300 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin maintenance treatment (Section 5.2.3.3). Subjects who do not reach the 300 mg/day dose within 40 weeks of day 1 will discontinue early from the study (Section 5.3).

Table 3: Up-Dosing Dose-Escalation Schedule (1-300 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	-	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. Maintenance visits will occur every 4 weeks for approximately 12 weeks. Dose adjustments may be allowed (Section 8.7.3.2, Section 8.7.4). The maintenance period may be extended by up to an additional 4 weeks to

accommodate dose adjustments during the last 2 weeks of maintenance. Study product will be administered under medical supervision at the study site during maintenance visits; subsequent maintenance doses will be administered daily at home as tolerated.

An exit DBPCFC will be performed at the end of maintenance, followed by an open baked whole egg food challenge within 14 days after the second day of the exit DBPCFC (Section 9.1.1, Section 9.1.2, Appendix 1, Appendix 2, Appendix 5). The 300 mg daily dose of study product must be tolerated for approximately 2 consecutive weeks before having the exit DBPCFC. In exceptional circumstances when the 300 mg daily dose is not taken for approximately 2 consecutive weeks before the planned exit DBPCFC for reasons unrelated to the study product, the medical monitor should be contacted to determine whether the exit DBPCFC is to be attempted. Discussion with the medical monitor is required to determine whether the exit DBPCFC and/or open baked whole egg food challenge may be attempted if the food challenge is delayed due to circumstances that create a safety risk (eg, an intercurrent illness).

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 approximately 9 months of overall treatment (initial dose escalation, up-dosing, and maintenance), including at least 4 weeks at 300 mg/day. 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). For a subject who discontinues early from the study, study treatment assignment will be unblinded after the study is completed.

Subjects with unresolved adverse events at early discontinuation or who had GI adverse events of interest (Section 8.7.6.2.1) 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
Protocol/ Investigator-Initiated	
Adverse event or intercurrent illness	Subjects must discontinue early for any intolerable adverse event that may lead to undue risk if study treatment were continued, such as the following: • Life-threatening symptoms, including anaphylaxis resulting in hypotension, neurologic compromise, or mechanical ventilation related to study treatment or food challenge. • Severe dose-related symptoms 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. Subjects must discontinue early for any adverse event that meets the early discontinuation criteria for study product tolerability or delays as follows: • Tolerability of study product: – Dose-limiting or moderate symptoms at ≤ 1 mg or severe symptoms at any dose on initial dose-escalation day 1; dose-limiting, moderate, or severe symptoms on initial dose-escalation day 2 – Unable to reach the 300 mg/day dose 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 ≤ 1 mg study product or for severe symptoms at the 2 mg dose on initial dose-escalation day 1 or 2 – Treatment with 3 or more doses of epinephrine for an event of dose-related symptoms anytime • Dose adjustment of study product: – Unable to escalate the dose level after 3 consecutive failed attempts with at least 2 weeks between each escalation attempt – Unable to tolerate 3 attempts at dose reduction after mild or moderate symptoms, or unable to tolerate 1 attempt at dose reduction after severe symptoms • Missed ≥ 15 consecutive days of study product dosing due to any circumstances (eg, as part of the treatment for an intercurrent adverse event). Missed doses per dose adjustment guidelines in Section 8.7.3.2 are allowed. Subjects must discontinue early for 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: • Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma). • Development of biopsy-documented eosinophilic esophagitis.

Category Reason	Comment
Use of prohibited medication	Prohibited concomitant medications are listed in Section 7.4.
Pregnancy	Pregnancy will be followed to delivery or until termination of the pregnancy (Section 8.7.7.2).
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, pregnancy, death, or noncompliance do not apply and the subject or 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 8.7.5).
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. Do not select this category if any other category applies.
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.

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 and attempting the open baked whole egg food challenge, will be considered as completing the study. Eligible subjects will have the option to enroll in an open-label, follow-on study to receive AR201 treatment until it becomes commercially available or product development is terminated. Blinded study treatment may continue in this study if the follow-on study is not yet available at the study site when subjects complete their course of treatment. The treatment assignment for each subject will be unblinded after study exit, after all major data

queries for the subject are resolved, and the open-label follow-on study is available at the study site.

Subjects with unresolved adverse events at 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 8.7.6.2.1) 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 8.7.6.2.1). 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 30 days or until consent for follow-up is withdrawn.
- Subjects who have unresolved serious adverse events at early discontinuation or study exit will have safety follow-up for 30 days or until the ongoing serious 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 8.7.6.2.1) 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 subjects or parent/caregivers who do not respond to telephone calls (Section 5.6).

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

For subjects who had adverse events of interest (ie, GI adverse events that result in dose interruption > 7 consecutive days or early discontinuation; Section 8.7.6.2.1), subjects aged ≥ 8 years and parents/caregivers of subjects aged 4 to 18 years will complete the Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0) questionnaire while the subject is symptomatic, at early discontinuation or study exit, and monthly for the duration of safety follow-up. The PEESS v2.0 results are to be reviewed by the investigator. If the PEESS v2.0 results suggest the subject is experiencing symptoms consistent with EoE, the investigator should monitor the symptoms and use clinical judgment to determine whether referral to a gastroenterologist is needed for further evaluation or treatment.

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 subject or parent/caregiver of any applicable subject 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 or 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 AR201 and placebo.

The sponsor will provide AR201 and placebo capsules.

6.2 Study Product Characteristics

The AR201 drug product consists of dried egg white with excipients, including pregelatinized starch, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide (colloidal silicon dioxide is used in the 12 to 300 mg dosage strengths only). The drug product powder is supplied in color-coded pull-apart hypromellose capsules at 13 dosage strengths (0.2, 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, or 300 mg egg white protein). The 0.2 mg capsule shells are white and the 1 to 300 mg capsule shells are grey and blue-green. The dosage strength is printed on the capsule shell in an edible ink for all dosage strengths except 0.2 mg.

Placebo is formulated with the inactive ingredients used in AR201, and without dried egg white. Placebo contains inactive ingredients to match the color and texture of dried egg white, and will be provided as capsules identical to the AR201 test product capsules.

Additional details will be provided in the pharmacy manual.

6.2.1 Packaging of Study Product

Capsules containing study product (AR201 or placebo) are packaged in white 50 mL high-density polyethylene bottles with a 1 g desiccant pouch and an induction-sealed child resistant cap. Each bottle contains 21 capsules of study product (AR201 or placebo), which 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.

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. 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 bottle containing study product for the assigned dose level and administered under medical supervision at the study site. Once a dose is removed from the bottle containing study product, the bottle must be dispensed to the subject or 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, bottles containing study product cannot be used for any other dosing interval or any other subject. Subjects or parents/caregivers will be instructed to store the bottles containing study product in the refrigerator, document all doses taken at home in a diary, and return unused study product 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 bottle of study product may be dispensed on a case-by-case basis after submission of a documented request and medical monitor approval. One additional bottle containing study product 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 decrease the threshold at which allergic reactions may occur following allergen exposure (eg, exercising or taking hot showers or baths) within 3 hours after dosing.
- For subjects engaging in strenuous exercise before the planned dosing time, dosing should be delayed until any signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.
- Dosing should not occur within 2 hours before bedtime.
- In case of illness or symptoms such as wheezing, worsening asthma, vomiting, or diarrhea, the subject or parent/caregiver is to notify the study site of the symptoms and for possible dose adjustments before dosing with study product.

Dose Preparation

The same procedures will be followed for preparing and administering study product at the study site or at home. Study site doses may be prepared by site staff, the subject, or the parent/caregiver under direct supervision of study site staff for training purposes. Doses at home will be prepared by the subject or supervising adult using a vehicle food (eg, applesauce, 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. 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 2 hours after mixing into a vehicle, the mixture should be discarded and a new dose prepared.

The dose should be administered at the same time each day (ideally within a 4-hour period). 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.

Subjects must take their dose following their assigned dosing schedule, except when dose modifications are needed due to adverse events or other reasons (Section 8.7.3, Section 8.7.4).

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 8.7.5.

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 will be performed to document compliance with the dosing regimens; noncompliance may lead to early discontinuation (Section 5.3). Subjects or parents/caregivers will be asked to 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, to study visits for reconciliation with the diary. Study site personnel must make reasonable efforts to obtain study product packaging and any unused capsules from subjects or 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 screening 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 these medications or their effect on the cardiovascular system may reduce the ability of the subject to respond appropriately to rescue medication used for an allergic reaction or increase the risk of adverse reactions after epinephrine administration. Additionally, epinephrine used as treatment for 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. Use of prophylactic antihistamines during initial dose escalation is not allowed.

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 discussion with 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 ≤ 3 weeks during the study. Topical steroid use is allowed after an SPT and during the study.

7.3 Rescue Medications

All rescue medications (ie, any medication used as treatment for 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 as treatment for individual acute allergic reactions (eg, antihistamine, epinephrine, IV fluids, beta-adrenergic agonist [eg, albuterol by inhaler or nebulizer], oxygen, glucocorticosteroids) are to be used following routine medical practice.

An epinephrine auto-injector device will be provided or prescribed as appropriate to subjects or 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	
Angiotensin-converting enzyme inhibitors	
Beta-blockers (oral)	
Calcium channel blockers	
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.
Allergen immunotherapy in the build-up phase	May not be used within 6 months before screening or initiated during the study.
Tricyclic antidepressants	

Ig, immunoglobulin; IL, interleukin.

8 SAFETY CONSIDERATIONS

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

Study assessments of safety include adverse events, physical examinations, vital signs, peak expiratory flow (PEF), 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 frequency and severity of adverse events and serious adverse events. 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. The medical monitor should be notified if emergency unblinding is occurring or before unblinding if possible.

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 or natural disease progression, in the nature, severity, frequency, or duration of a pre-existing condition.
- An investigational abnormality (eg, PEF/FEV_1 measurements, laboratory tests, vital signs) **only if the abnormality is considered clinically significant** by the investigator (eg, associated with clinically significant symptoms, requires additional diagnostic testing or intervention, leads to change in study product dosing or discontinuation from the study). 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.
Inpatient hospitalization or prolongation of existing hospitalization	Does not include hospitalization for extended observation (eg, to watch for a delayed or biphasic reaction) or planned hospitalization (eg, for an elective procedure).
Disability or permanent damage	Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
Congenital abnormality or birth defect	
Important medical event	An event that may jeopardize the health of the subject or require medical or surgical intervention to prevent any of the other outcomes. In general, anaphylaxis classified as an important medical event should require an emergency department visit with intensive therapy (determined by the investigator, but may include interventions such as intravenous epinephrine, intubation, or admission to an intensive care unit; 1-2 intramuscular injections of epinephrine are typically not considered intensive therapy). If a systemic allergic reaction of mild or moderate severity and without administration of intensive therapy is reported as an important medical event, a clinical assessment by the investigator and reason for the assessment must be included in the event narrative.

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

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

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 8.7.6.

8.4 Definition of Systemic Allergic Reaction

The protocol criteria for systemic allergic reaction are provided in Table 7.

Adverse events of systemic allergic reaction assessed as grade 2 or higher per the systemic allergic reaction grading system (Section 8.6) are considered adverse events of interest and require rapid reporting as described in Section 8.8.2.

Table 7: Protocol Criteria for Systemic Allergic Reaction

Nonlocalized reaction [1] following allergen exposure and one or more of the following signs or symptoms: 1. Upper respiratory: laryngeal edema with stridor 2. Lower respiratory: wheezing, chest tightness, dyspnea, cyanosis, hypoxemia 3. Cardiovascular: clinically significant hypotension [2] And/or Nonlocalized reaction [1] following allergen exposure and signs and symptoms from 2 or more body systems as follows: 1. Cutaneous: generalized pruritus, generalized urticaria, generalized flushing, angioedema 2. Conjunctival injection or pruritus 3. Gastrointestinal: nausea, abdominal pain, vomiting, diarrhea 4. Respiratory: rhinitis, cough, laryngeal edema, wheezing, chest tightness, dyspnea, cyanosis, hypoxemia 5. Cardiovascular: clinically significant hypotension [2]

[1] The site of allergen exposure should be considered during the assessment of a systemic versus local reaction (Cox, 2017).

[2] 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 defined as follows:
- Age 1-10 years: < (70 mm Hg + [2 × age])
- Age 11-17 years: < 90 mm Hg

Adults: (age ≥ 18 years): systolic blood pressure < 90 mm Hg or > 30% decrease from baseline

8.4.1 Assessment of Anaphylaxis

Anaphylaxis is a severe, potentially life-threatening systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance (Sampson, 2006). The definition of anaphylaxis is met when any of the 3 criteria for suspected anaphylaxis in Table 8 are fulfilled and the adverse event is grade 3 or higher per the systemic allergic reaction severity grading system (Section 8.6).

Systemic allergic reactions that do not meet both the criteria in Table 8 and severity grade ≥ 3 per the systemic allergic reaction grading system (Section 8.6) will not be defined as anaphylaxis.

Adverse events of anaphylaxis are considered adverse events of interest and require rapid reporting as described in Section 8.8.2.

Table 8: Protocol Criteria for Definition of Anaphylaxis

1. Acute onset of an illness (minutes to hours) with involvement of the following: • Skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips/tongue/uvula) and at least 1 of the following:	a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) b. 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):	a. Involvement of the skin/mucosal tissue (eg, generalized hives, itch/flush, swollen lips/tongue/uvula) b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced blood pressure or associated symptoms (eg, hypotonia, syncope, incontinence) d. Persistent gastrointestinal 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:	a. Infants and children: > 30% decrease from baseline in systolic blood pressure or low systolic blood pressure defined as follows: – Age 1-10 years: < (70 mm Hg + [2 × age]) – Age 11-17 years: < 90 mm Hg b. Adults (age ≥ 18 years): systolic blood pressure < 90 mm Hg or > 30% decrease from baseline

Source: Adapted from Sampson, 2006.
The definition of anaphylaxis is met when any of the 3 criteria for suspected anaphylaxis are fulfilled and the adverse event is grade 3 or higher per the systemic allergic reaction severity grading system (Table 9).
PEF, peak expiratory flow.

8.5 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.

8.6 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.

Two different severity grading systems will be used depending on type of adverse event: systemic allergic reactions including anaphylaxis, or all other adverse events. Brief descriptions of the 2 severity grading systems are provided.

Severity of systemic allergic reactions, including anaphylaxis, will be graded using the systemic allergic reaction grading system, with scores ranging from 1 (mild) to 5 (death) (Table 9). The protocol criteria for systemic allergic reaction are provided in Section 8.4. The term *anaphylaxis* is used to describe the subset of systemic allergic reactions that meet the criteria in Table 8 and are grade 3 or higher per the systemic allergic reaction grading system (Table 9). The clinical assessment of anaphylaxis is described in Section 8.4.1.

Table 9: Systemic Allergic Reaction Grading System

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death
Systemic allergic reaction including any of the following signs and symptoms from 2 or more body systems: • Cutaneous: generalized pruritus, generalized urticaria, generalized flushing, angioedema (not laryngeal) • Conjunctival injection or pruritus • Upper airway: rhinitis, cough (unrelated to laryngeal edema or bronchospasm) • Gastrointestinal: nausea, mild abdominal pain, vomiting, or diarrhea	Systemic allergic reaction involving 1 or more of the following: • Lower airway (wheezing, chest tightness, dyspnea) • Gastrointestinal: moderate abdominal pain or persistent vomiting or diarrhea	Systemic allergic reaction involving 1 or more of the following: • Upper airway: laryngeal edema with stridor • Lower airway (wheezing, chest tightness, dyspnea) with cyanosis or hypoxia (O_2 saturation ≤ 92%) • Cardiovascular: clinically significant hypotension [1] without end-organ dysfunction	Systemic allergic reaction involving 1 or more of the following: • Lower airway: respiratory compromise (dyspnea, wheeze, bronchospasm, hypoxemia) requiring mechanical support • Cardiovascular: hypotension [1] with associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope)	Death

The protocol criteria for systemic allergic reaction are provided in Section 8.4. The site of allergen exposure should be considered during the assessment of a systemic versus local reaction.

[1] 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 defined as follows:
– Age 1-10 years: < (70 mm Hg + [2 × age])
– Age 11-17 years: < 90 mm Hg
Adults: (age ≥ 18 years): systolic blood pressure < 90 mm Hg or > 30% decrease from baseline

Severity of all other adverse events (including adverse events considered allergic reactions that are not systemic allergic reactions) will be graded according to the general adverse event grading system. Adverse events will be graded 1 to 5 and have unique clinical descriptions of severity for each adverse event based on the general guideline presented in Table 10. Full details of the general adverse event grading system are provided in the study manual.

Table 10: General Adverse Event Grading System

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death
Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Severe symptoms causing inability to perform usual social and functional activities with intervention	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or hospitalization indicated	Death

8.7 Special Safety Considerations

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

8.7.1 Assessment of Allergic Reactions

Allergy symptoms (allergic reactions) are expected during treatment with study product, consistent with other desensitization studies. Subjects must be observed for at least 90 minutes after completion of a dose or dose escalation at the study site, with measurements of blood pressure and heart rate, and assessment for symptoms of allergic reaction performed 15 to 30 minutes postdose and approximately every 30 minutes thereafter.

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

- Mild symptoms: observe for 90 minutes or at least 1 hour after symptoms resolve, whichever is longer.
- Moderate symptoms: observe for at least 2 hours after symptoms resolve.

- Severe symptoms: observe for at least 3 hours after symptoms resolve either at the study site or an emergency facility, as appropriate. Consider extended overnight observation 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.

The assessing physician will determine whether the allergy symptoms meet the criteria for dose-limiting symptoms (Section 8.7.1.1).

The severity of symptoms of an allergic reaction will be assessed as described in Section 8.6.

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

8.7.1.1 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 (allergic reactions) 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 11.

Table 11: Allergy Symptom Severity and Study Product Dose Tolerability

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

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

Mild symptoms: For a study product dose associated with mild symptoms, investigator assessment is essential in determining if the symptoms are dose limiting. 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 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 antihistamine or ≥ 1 dose of epinephrine
- Progress in severity or distribution over time
- Do not resolve or show definite signs of resolving in under 1 hour
- 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 in the subject's source documents.

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. Isolated mild oropharyngeal pruritus occurring ≥ 7 times within 2 weeks may not lead to an assessment of not tolerated for the dose level; tolerability of the dose level should be discussed with the medical monitor.

Moderate symptoms: A study product dose associated with moderate 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 symptoms will be assessed as not tolerated.

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

8.7.2 Treatment of Allergic Reactions After Study Product Dosing

Treatment of allergic reactions after study product dosing is guided by the type of symptoms and severity as determined by the investigator and should follow routine medical practice and professional practice guidelines, including the prompt use of epinephrine when indicated. Symptomatic treatment should be used to supplement dose reduction and not as a substitute for it. Rescue medications for acute allergic reactions include antihistamines, epinephrine, IV fluids, beta-agonists (eg, albuterol by inhaler or nebulizer), oxygen, and glucocorticosteroids as indicated (Section 7.3). 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 discussion with the medical monitor.

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

8.7.3 Dose Adjustment of Study Product for Allergic Reactions

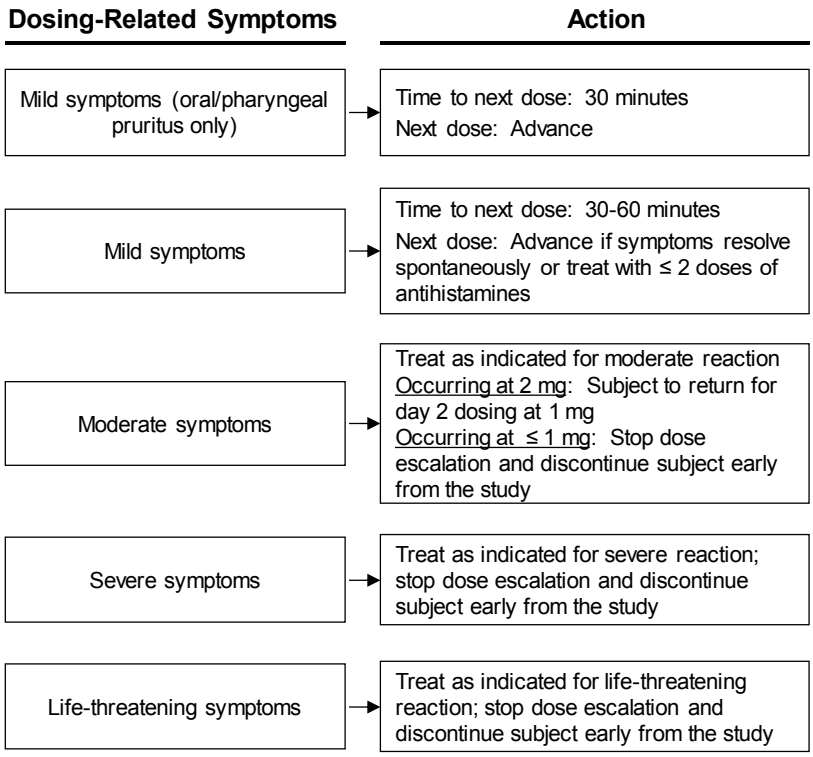
8.7.3.1 Dose Adjustment of Study Product During Initial Dose Escalation (Days 1 and 2)

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

- Extend the time interval between study product doses (up to an additional 30 minutes) without any additional treatment.
- Initiate enhanced clinical monitoring (eg, more frequent vital sign monitoring [including respiratory rate], auscultation, oxygen saturation level).
- 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 ≤ 1 mg study product or for severe symptoms at the 2 mg 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 symptoms on initial dose-escalation day 1 is shown in Figure 2 and described in Table 12. The same process algorithm for actions to be taken with study product dosing and treatment for acute symptoms is to be followed for allergic reactions occurring on day 2 of initial dose escalation, with the exception that only 1 dose will be administered on day 2.

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



Assess dose tolerability per Section 8.7.1.1.

Table 12: Description of Actions to Be Taken With Study Product Dosing for Allergy Symptoms on Initial Dose-Escalation Day 1

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

Assess dose tolerability per Section 8.7.1.1.

Treatment with epinephrine, beta-agonist, oxygen, IV fluids, > 2 doses of antihistamines, and/or glucocorticosteroids at ≤ 1 mg study product or for severe symptoms at the 2 mg dose on initial dose-escalation day 1 or 2 will stop the initial dose escalation and discontinue the subject early from the study (Section 5.3).

IV, intravenous.

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

Actions that may be taken with study product dosing for dose-related allergic reactions during up-dosing and maintenance are guided by the severity of the allergic reactions and include the following:

- Administer the next dose of study product at the study site under medical supervision.

- Delay the study product dose escalation an additional 1 to 2 weeks.
- Reduce the study product dose level by 1 or 2 dose levels (study product dose levels are provided in Table 3).
- 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 13.

When study product dose-related allergy symptoms occur at home, the subject or 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 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 8.7.1.1).

In general, a reduced dose of study product is to be given at the study site under medical supervision and continued for 1 to 2 weeks at home. The lowest dose level of study product for dose adjustments is 1 mg.

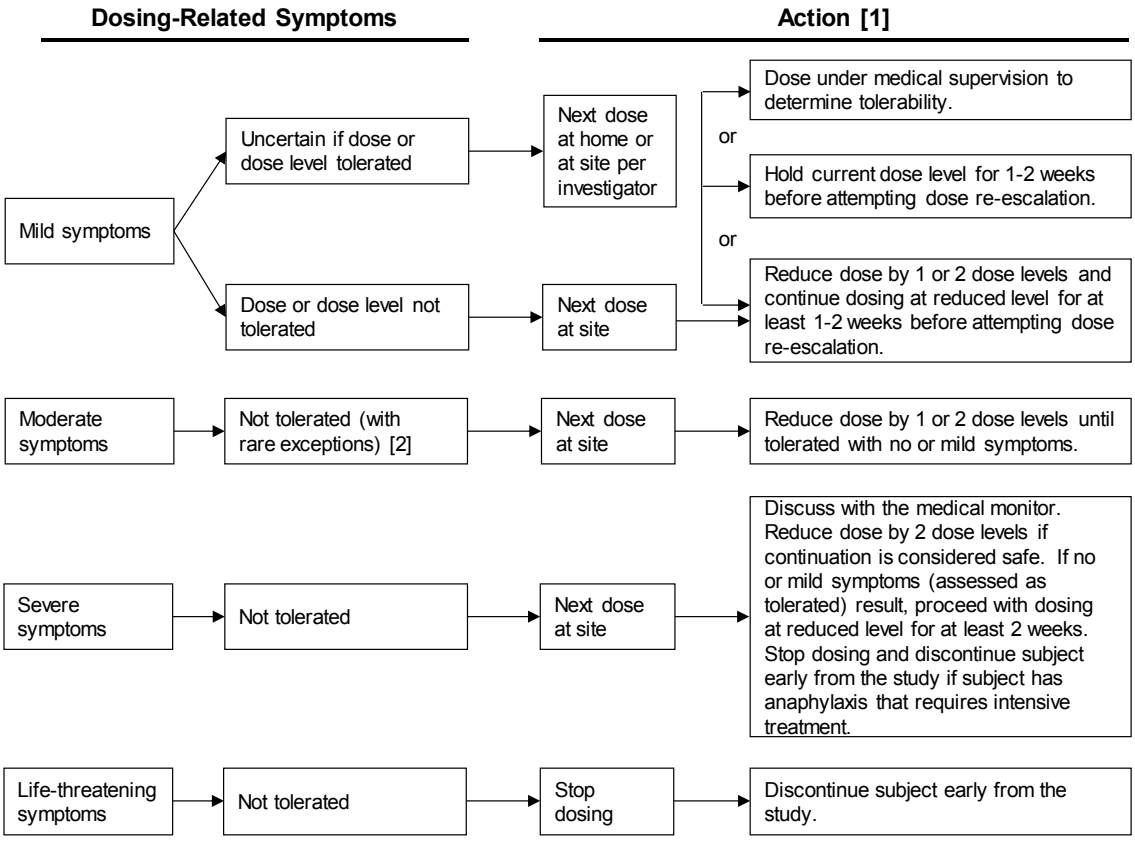
Symptomatic treatment should be used to supplement dose reduction and not as a substitute for it. Symptomatic treatment of adverse events should be discontinued before attempting dose re-escalation at the study site. However, if treatment for chronic or recurrent adverse events cannot be withdrawn successfully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

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

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

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



Assess dose tolerability per Section 8.7.1.1.

[1] Guidelines for dose adjustment after administration of antihistamines and/or epinephrine for dose-related allergy symptoms of any severity are provided in Table 14.

[2] 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 13).

Table 13: Description of Actions to Be Taken With Study Product Dosing for Dose-Related Allergy Symptoms During Up-Dosing and Maintenance

Symptoms	Actions
Mild	For oral/pharyngeal pruritus occurring in isolation, continue the study product dose level at home for the 2-week dosing interval, unless other symptoms develop. For other mild symptoms and if the study product dose is assessed as tolerated (Section 8.7.1.1), 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 8.7.1.1), the next dose is to be the previous tolerated dose level and given at the study site. • If the reduced dose is tolerated, continue the dose level for at least 1 to 2 weeks. • If the reduced dose is assessed as not tolerated, the next dose is to be reduced 1 or 2 dose levels and given 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 8.7.1.1). • Recurrent, isolated mild oropharyngeal pruritus occurring ≥ 7 times within 2 weeks may not lead to an assessment of not tolerated for the dose level; tolerability of the dose level should be discussed with the medical monitor. Other actions that may be taken for chronic or recurrent mild symptoms: • Continue daily dosing at home at the current dose level. • 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).

Symptoms	Actions
	GI symptoms For chronic or recurrent GI symptoms, especially upper GI symptoms, a low threshold for study product dose reduction and for considering early discontinuation is recommended due to the potential for eosinophilic esophagitis. For dose-limiting chronic or recurrent GI symptoms, follow the general guidance in this table based on symptom severity.
Moderate	Administer the previous tolerated dose of study product at the study site at the time of the next dose. • 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 in the subject's source documents.
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 at the time of the next dose 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). If the symptoms were associated with a modifiable risk factor that has resolved, the dose may be reduced by 1-2 dose levels at investigator discretion. Stop study product dosing and discontinue the subject early from the study if the subject has anaphylaxis that requires intensive treatment.
Life-threatening	Stop study product dosing and discontinue the subject early from the study (Section 5.3).

Assess dose tolerability per Section 8.7.1.1.
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/or epinephrine for dose-related allergy symptoms, including anaphylaxis, at the study site or at home during up-dosing and maintenance is described in Table 14.

Table 14: Dose Adjustment of Study Product After Treatment With Antihistamines and Epinephrine for Dose-Related Allergy Symptoms During Up-Dosing and Maintenance

Medications	Action
Antihistamines	Continue study product up-dosing if symptoms only require antihistamines. If symptoms during up-dosing at the study site or at home require > 2 doses of antihistamine alone or in combination with other medications, 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 epinephrine is required for dose-related allergy symptoms, including anaphylaxis, give the next dose of study product at the study site under medical supervision. The dose should be reduced by 1 or 2 dose levels at the discretion of the investigator based on the type and severity of the symptoms (Figure 3, Table 13). After continuing the reduced dose for a duration of time recommended by the investigator, dose re-escalation at 1 dose level may be attempted at the study site. If epinephrine is administered for severe symptoms, discussion with the medical monitor is required. If epinephrine is administered 3 or more times for an event of dose-related symptoms or anaphylaxis, stop study product dosing and discontinue the subject early from the study (Section 5.3). If epinephrine is given at home, recommend that subjects be taken to the nearest emergency department immediately.

8.7.4 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. In addition, the study product dose level may be temporarily reduced for decreased study product tolerability during menses.

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

If the dose is reduced for reasons other than allergic reactions to study product, the reduced dose will be given until the subject is 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 15. 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 8.7.5).

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

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

Table 15: Study Product Dose Re-Escalation After Dose Reduction for Reasons Other Than Allergic Reactions

Duration of Dose Reduction	Action
1-2 consecutive days	Next dose at the previous dose level at home and continue the dose level for 2 weeks.
3-4 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 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 1 dose level above. If re-escalation is tolerated, continue the dose level for at least 2 weeks before attempting re-escalation.

8.7.5 Missed Doses During Up-Dosing and Maintenance

Missed doses of study product can pose a significant risk to subjects anytime during the study, and the greatest risk is considered to be during up-dosing. Procedures for missed consecutive doses of study product during up-dosing and maintenance are described in Table 16.

Table 16: Procedures for Missed Consecutive Doses of Study Product

Missed Doses [1]	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%-70% (rounded down to the nearest feasible whole dose) of last tolerated dose under medical supervision at the study site at investigator discretion. • 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 8.7.3.2).
> 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 dosing under medical supervision at the study site as follows: • If the missed doses occurred at a dose level of ≤ 120 mg, reinitiate next dose at approximately 25% (rounded down to the nearest feasible whole dose) of last tolerated dose. • If the missed doses occurred at a dose level of ≥ 160 mg, dosing may be reinitiated at the nearest whole dose that is approximately 25%-50% of the last tolerated dose, at the discretion of the investigator. • 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 8.7.3.2).
≥ 15 consecutive days	Stop study product dosing and discontinue the subject early from the study (Section 5.3).

[1] For missed doses at the 1 mg dose level, reinitiate next dose at 1 mg at home or at the study site depending on the duration of missed doses.

8.7.6 Adverse Events of Interest

Adverse events of interest include systemic allergic reactions assessed as grade 2 or higher (including anaphylaxis), GI adverse events with prolonged dose interruption (> 7 consecutive days) or that result in early discontinuation, accidental and nonaccidental food allergen exposure, adverse events with severe symptoms, and use of epinephrine. These events require rapid reporting as described in Section 8.8.2.

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

8.7.6.1 Systemic Allergic Reactions Assessed as Grade 2 or Higher, Including Anaphylaxis

The protocol criteria for systemic allergic reaction are provided in Table 7. The assessment of anaphylaxis is described in detail in Section 8.4.1. Adverse events of systemic allergic reaction assessed as grade 2 or higher per the systemic allergic reaction grading system (Section 8.6), including anaphylaxis (ie, grade ≥ 3 per the systemic allergic reaction severity grading system [Table 9] and meets the protocol-specified criteria for anaphylaxis [Table 8]), are considered adverse events of interest and require rapid reporting as described in Section 8.8.2.

8.7.6.2 GI Adverse Events

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 13). 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.

8.7.6.2.1 GI Adverse Events of Interest

GI adverse events of interest are as follows:

- GI adverse events leading to prolonged dose interruption, defined as withholding study product for > 7 consecutive days due to GI adverse events anytime during the study
- GI adverse events that result in early discontinuation

GI adverse events of interest require rapid reporting as described in Section 8.8.2. Subjects aged ≥ 8 years and parents/caregivers of subjects aged 4 to 18 years will be asked to

complete the PEESS v2.0 questionnaire while the subject is symptomatic and thereafter at intervals as described in Section 5.5.1. Additional information about the PEESS v2.0 questionnaire is provided in Section 9.3.4.

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

8.7.6.3 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 egg, 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 egg, 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 8.8.2.

Subjects and 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.

8.7.6.4 Severe Adverse Events

Adverse events assessed by investigators as severe by either of the 2 severity grading systems (systemic allergic reaction grading system or general adverse events grading system, Section 8.6) are considered adverse events of interest and require rapid reporting as described in Section 8.8.2. Severe allergy symptoms will result in early discontinuation during initial dose-escalation days 1 and 2 (Table 12) and may result in early discontinuation during up-dosing and maintenance (Table 13).

8.7.6.5 Adverse Events Requiring Use of Epinephrine

Adverse events, especially allergic reactions, may result in epinephrine use, as described in Section 8.7.2. Adverse events requiring use of epinephrine are considered adverse events of interest and require rapid reporting as described in Section 8.8.2.

8.7.7 Other Notable Events

Other notable events include overdose and pregnancy.

8.7.7.1 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.

8.7.7.2 Pregnancy and Other Reproductive Considerations

Egg OIT may increase the risk of allergic reactions, including anaphylaxis. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus during pregnancy. In addition, the effect of egg OIT on the immune system of the mother and fetus during pregnancy is unknown. Therefore, all female subjects of childbearing potential must have a negative serum pregnancy test before the first dose of study product and a negative urine test during the treatment period and must avoid pregnancy during the study.

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

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

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

8.8 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.

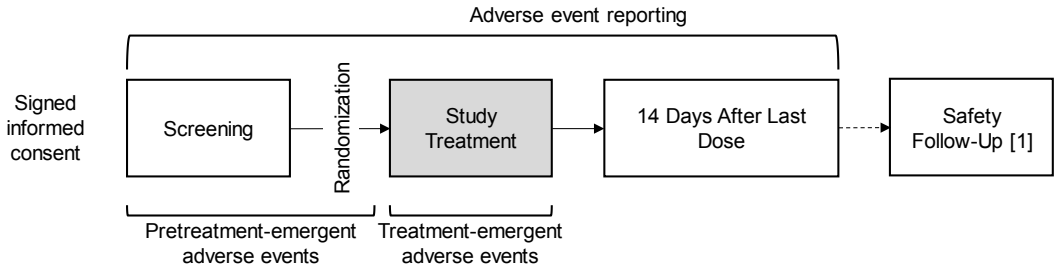
All signs and symptoms associated with an adverse event, whether or not related to the study product, must be fully and completely documented **for all subjects** (ie, both treatment groups) on the adverse event case report form and in the subject's source documents. In addition, any adverse event resulting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

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

8.8.1 Adverse Event Reporting Period

Collection and reporting of adverse event information will begin at the time the screening informed consent/assent form is signed and will continue for all subjects through 14 days after the last dose of study product, or through study exit for subjects receiving AR201 treatment in a follow-on study (Figure 4).

Figure 4: Adverse Event Reporting Period



[1] 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.

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

Serious adverse events and adverse events of interest for **all subjects** (ie, both treatment groups) require rapid reporting **within 24 hours** of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study product.

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

- Study number (AIME01)
- Site name and number
- Investigator name
- Subject ID number, sex, and age (unless omitted per local regulations)
- Details of study treatment
- The date of the report
- A description of the event (event term, severity)

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

8.8.2.1 Serious Adverse Events Reporting

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

If a subject dies, the serious adverse event report should include the cause of death as the event term (with fatal outcome), whether the event leading to death was related to study product, the autopsy findings if available, and any other supporting data (eg, death certificate, hospital/study site notes). The study site should also report the death to the sponsor by telephone.

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

8.8.2.1.1 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 requirements including but not limited to ICH E6 and ICH E2F.

8.8.2.2 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:

- Systemic allergic reactions assessed as grade 2 or higher, including anaphylaxis (Section 8.4 and Section 8.4.1).
- 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 8.7.6.2.1).
- Accidental/nonaccidental food allergen exposure (Section 8.7.6.3). Rapid reporting is required regardless of whether the exposure resulted in an adverse event.
- Severe adverse events (Section 8.7.6.4). Intended for adverse events that do not meet the criteria for other adverse events of interest.
- Use of epinephrine (Section 8.7.6.5). Use of epinephrine for a serious adverse event or other event requiring rapid reporting (eg, grade 2 or higher systemic allergic reaction, food allergen exposure) does not need to be reported separately.

Adverse events of interest meeting serious adverse event criteria are to be reported as serious adverse events.

8.8.2.3 Other Notable Events Reporting

Although pregnancy is not considered an adverse event, pregnancy must be reported on a pregnancy notification form. The pregnancy will be followed to delivery or termination, and reporting the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9 ASSESSMENT OF EFFICACY, SAFETY, AND HEALTH-RELATED QUALITY OF LIFE

9.1 Measures of Desensitization

9.1.1 Double-Blind Placebo-Controlled Food Challenge

The screening and exit DBPCFCs will each be conducted over 2 days and consistent with accepted food challenge procedures. Single doses of dried egg white 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.

9.1.2 Open Baked Whole Egg Food Challenge

The screening and exit open baked whole egg food challenges will be conducted within a single day and consistent with accepted food challenge procedures.

The open baked whole egg food challenge will conditionally test single doses of baked egg protein using a baked food product with egg (portions of 1 muffin equivalent to approximately 125, 250, 500, 500, and 625 mg baked egg protein), administered sequentially at 20- to 30-minute intervals up to a single highest dose of 625 mg of baked egg protein (cumulative 1 muffin that contains approximately one-third of one whole egg [equivalent to approximately 2000 mg baked egg protein]). The open baked whole egg food challenge is described in Appendix 2, including all requirements before, during, and after the open baked whole egg food challenge. Full details are provided in the study manual.

9.2 Skin Prick Test

Egg white SPT mean wheal diameters will be measured to assess the immunomodulatory effects of study treatment. SPTs will include a positive control (histamine) and negative control (saline). SPT to aeroallergens (standard panel per local medical practice) will be performed at screening only. SPTs for egg white 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.

9.3 Safety and Other Assessments

9.3.1 Lung Function Tests and Assessments of Asthma Control

Lung function tests will be performed according to the schedules of activities (Appendix 4, Appendix 5). Lung function tests include PEF for subjects aged ≥ 6 years and attempts of PEF for subjects aged 4 to 5 years. Spirometry will be performed if PEF shows a clinically

relevant reduction or for symptoms of clinical deterioration (eg, active wheeze on physical examination). Spirometry will be performed at screening for subjects aged ≥ 6 years with asthma.

For subjects with asthma, the evaluation of asthma severity will be assessed using the classification in Table 17.

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

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

Table 17: Evaluation of Asthma Based on NHLBI Criteria

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

Adapted from NHLBI, 2007.

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

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

9.3.2 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.

9.3.3 TNSS Questionnaires

The Total Nasal Symptom Score (TNSS) is used to assess the severity of allergic rhinitis and will be administered only to subjects with pre-existing allergic rhinitis. The TNSS (short form) consists of 3 questions that address nasal obstruction, rhinorrhea, and nasal itch/sneezing (Downie, 2004). Each question has a choice of 4 responses that range from 0 (no symptoms) to 3 (severe symptoms). The subject is asked to recall symptoms over the last week to allow calculation of the symptom score.

9.3.4 PEESS v2.0 Questionnaire

The PEESS v2.0 (Martin, 2015; Franciosi, 2011) is used to assess the frequency and severity of EoE symptoms in the last month and will be administered only for subjects with GI adverse events of interest (Section 5.5.1, Section 8.7.6.2.1). 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 of a subject aged 4 to 18 years completes the Parent Report for Children and Teens, and subjects aged ≥ 8 years complete the Children and Teens Report.

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

9.3.5 Physical Examinations and Vital Signs

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

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

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

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

9.4 Health-Related Quality of Life Assessments

Health-related quality of life of subjects with hen egg allergy treated with AR201 or placebo will be assessed using scores from the Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) questionnaires. FAQLQ and FAIM questionnaires will be completed according to the schedules of activities (Appendix 4, Appendix 5).

The FAQLQ family of self- and proxy-report instruments is used to assess the effect of food allergy on the subject's quality of life. Evaluations by the subject and parent/caregiver (as applicable) use different forms by subject age group (van der Velde, 2011; Flokstra-de Blok, 2009a; Flokstra-de Blok, 2009b; DunnGalvin, 2008; Flokstra-de Blok, 2008). The number of items and domains vary by the instrument administered, and each item is scored on a 7-point scale from 1 (no impact) to 7 (extreme impact).

The FAIM self-report instruments are used to measure subject perception of food allergy severity and expectation of allergen exposure outcome, as evaluated by the subject using different forms by age group (van der Velde, 2010). The parent/caregiver versions include questions related to perception of disease severity and expectation of allergen exposure outcome for their child/teenager. The number of items and domains vary by the instrument administered, and each item is scored on a 7-point scale from 1 (limited severity perception) to 7 (greatest severity perception).

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 (AR201 or placebo). Randomization will be stratified by baseline reactivity (tolerant or intolerant) to baked egg in an open baked whole egg food challenge at screening. Subjects who tolerate approximately 2000 mg cumulative baked egg protein without dose-limiting allergy symptoms will be considered baked egg tolerant. Subjects who do not complete the screening open baked whole egg food challenge for reasons other than dose-limiting symptoms and who have a clear clinical history of tolerance to baked egg may be considered baked egg tolerant after discussion with the medical monitor. All other subjects will be considered baked egg intolerant.

Data for demographic and baseline characteristics, efficacy, and safety will be summarized by treatment group (AR201 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 2-sided type I error of 0.05.

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 intent-to-treat (ITT) population (ie, full analysis set) will be defined as all subjects who receive any part of one 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 dried egg white 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.

The safety population will be defined as all subjects who receive any randomized study treatment (ie, who receive any part of one dose of study product and complete one 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 84 subjects randomly assigned at a ratio of 2:1 to AR201 or placebo (56 AR201, 28 placebo) provides 89% power to demonstrate a significant treatment difference of at least 35% in desensitization response rate with AR201 compared with placebo for the primary efficacy endpoint of the proportion of subjects tolerating an at least 1000 mg single dose of dried egg white protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on a 2-sided alpha of 0.05, and 2-sample comparison of binomial proportions with an assumed maximum desensitization rate of 60% in the AR201 group and 25% in the placebo group. Treated subjects who discontinue early from the study will be considered nonresponders.

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 AR201 treatment in subjects aged 4 to 26 years, inclusive, with hen egg allergy.

The primary efficacy endpoint is the proportion of subjects treated with AR201 compared with placebo who tolerate a single highest dose of at least 1000 mg dried egg white protein with no more than mild allergy symptoms at the exit DBPCFC.

The ITT population and the Cochran-Mantel-Haenszel test will be used for these analyses. Subjects tolerating an at least 1000 mg single challenge dose of dried egg white protein will be considered responders; subjects who do not tolerate an at least 1000 mg single challenge dose of dried egg white protein 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 for each stratum will be presented for each treatment group using Wald CIs. The 95% CI for the treatment difference (desensitization rate for AR201 treatment minus desensitization rate for placebo) will be constructed by combining the stratum-specific differences using the Cochran-Mantel-Haenszel weights.

Full details will be provided in the statistical analysis plan.

10.5.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be assessed as follows:

The proportion of subjects who tolerate a single highest dose of at least 300 mg dried egg white protein with no more than mild symptoms during the exit DBPCFC will be assessed using the methods described for the primary endpoint (Section 10.5.1).

The proportion of subjects who tolerate a single highest dose of at least 600 mg dried egg white protein with no more than mild symptoms during the exit DBPCFC will be assessed using the methods described for the primary endpoint (Section 10.5.1).

The maximum severity of allergy symptoms after consuming dried egg white protein during the exit DBPCFC will be assessed by tabulating the number and percentage of subjects by maximum severity of allergy symptoms at the exit DBPCFC and by treatment group. The Cochran-Mantel-Haenszel test stratified by baseline reactivity to baked egg in an open baked whole egg food challenge at screening 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 AR201 treatment in a follow-on study.

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 systemic allergic reaction grading system for systemic allergic reactions including anaphylaxis, and the general adverse events grading system for all other adverse events (Section 8.6). Anaphylaxis is defined as a severe, potentially life-threatening systemic allergic reaction (ie, grade ≥ 3 per the systemic allergic reaction grading system [Section 8.6]) that meets the criteria for anaphylaxis per Section 8.4.1.

Summaries of the safety of AR201 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 and severity of treatment-related adverse events
- 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 adverse events considered allergic reactions, systemic allergic reactions, 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 ACT, C-ACT, lung function data, EASI, TNSS, 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:

- Proportion of subjects who develop dose-limiting symptoms to approximately 2000 mg cumulative baked egg protein at screening and subsequently tolerate approximately 2000 mg cumulative baked egg protein with no more than mild symptoms at study exit
- Proportion of subjects who tolerate a single highest dose of 2000 mg dried egg white protein with no more than mild symptoms at the exit DBPCFC
- Maximum dose of dried egg white protein reached with no more than mild symptoms during the exit DBPCFC
- Change from baseline in the single highest tolerated dose of dried egg white protein at the exit DBPCFC
- Use of epinephrine as rescue medication at the exit DBPCFC compared with use at the screening DBPCFC
- Change from baseline in egg white-specific and egg white component serum immunoglobulins
- Change from baseline in mean wheal diameter on SPT to egg white
- Change from baseline in ACT/C-ACT, EASI, and TNSS scores
- Change from baseline in FAQLQ and FAIM scores

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, unless consent is obtained for longer storage.

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 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. No local laboratory data will be entered into the study database and local laboratories will not be included on Form FDA 1572.

Additional details are provided in the laboratory manual.

Table 18: Clinical Laboratory Tests

Hematology	Immunology	Other
Red blood cell count Hemoglobin Hematocrit Platelet count White blood cell count with differential (percent and absolute) • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Total immunoglobulin (Ig) E Egg white-specific and egg white component IgE Egg white-specific IgG4	Pregnancy test (serum at screening; urine thereafter) for all females of childbearing potential

12.2 Optional Blood Samples for Potential Future Substudies

Optional blood samples will be collected at certain study sites according to the schedules of activities (Appendix 4, Appendix 5) and stored for potential future studies in patients with food allergy and/or patients receiving egg OIT.

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 regulations 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 regulations as appropriate will be obtained from each subject or pediatric subject's parent/caregiver before entering the subject in this study. A properly executed age-appropriate assent form will also be obtained from each pediatric subject where required 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 to each subject or signed informed consent 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.

In the event of early study closure for reasons other than safety or quality, subjects who complete at least 9 months of study treatment, including at least 4 weeks at 300 mg/day, may have the exit DBPCFC and open baked whole egg food challenge and complete the study. Subjects must tolerate the 300 mg daily dose of study product for approximately 2 consecutive weeks before having the exit DBPCFC. Subjects who do not complete at least 9 months of study treatment, including at least 4 weeks at 300 mg/day, will discontinue early from the study.

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

Phase 2 Study of AR201 Oral Immunotherapy for Desensitization in Children, Adolescents, and Young Adults With Hen Egg Allergy

Signature of Agreement for AIME01 Protocol Amendment 3.0 – 28 May 2020

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, local applicable legislation, 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 dried egg white 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 consistent with the Practical Allergy (PRACTALL) guidelines for safety, assessment, and scoring (Sampson, 2012). The DBPCFC will use the dosing schedule shown in Table 1.

Table 1: Screening and Exit DBPCFC Challenge Doses

Timing	Dried Egg White Protein Dose (mg)	Cumulative Dose (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, beta-adrenergic agonists, and intravenous (IV) fluids.

PREPARATION FOR THE DBPCFC

Before the Day of the DBPCFC

Contact the subject and 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. Study site staff will contact the subject or 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 subject or 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.
- Instruct that the dose of study product is to be withheld on the days of the exit DBPCFC.
- Inform that female subjects of childbearing potential will have a urine pregnancy test before starting the DBPCFC on the first day of the 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.
   - Negative urine pregnancy test for all female subjects of childbearing potential.
   - No recent or active illnesses. Reschedule the DBPCFC if the subject is experiencing symptoms of an acute infection (eg, fever, recent nausea, vomiting, diarrhea) or any other illness that may interfere with the subject's safety or interpretation of the results. Do not conduct the 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).
4. Perform a focused physical examination to confirm adequate baseline. The examination should be sufficient to determine changes from baseline if signs or symptoms of an allergic reaction develop during the DBPCFC.
5. Obtain peak expiratory flow (PEF) measurement.
   - For subject aged ≥ 6 years, make 3 attempts and document them in the subject's source documents. The PEF must be at the subject's baseline value (based on the screening values) or at least 80% of the predicted value, assuming the value is obtained accurately with good effort. Reschedule the DBPCFC if the PEF does not meet one of these criteria or the investigator assesses the respiratory status as compromised.
   - For subject aged 4 to 5 years, attempt to measure PEF and document it in the subject's source documents (if unable to successfully obtain, record attempts and investigator assessment).
6. Place a saline lock if directed by the supervising physician for subjects considered at high risk of allergic reaction or severe reaction based on medical history.
7. Ensure rescue medications and resuscitation equipment are available and readily accessible, including epinephrine, diphenhydramine (oral, IV), cetirizine (oral), albuterol (nebulizer or as a metered dose inhaler), IV supplies and fluids, oxygen, and suction.
   - Calculate appropriate weight-based doses of emergency medications in advance for treatment of reactions.
   - Prepare an appropriate dose of epinephrine at a 1:1000 effective concentration for intramuscular use and have it readily accessible. An epinephrine auto-injector or epinephrine in ampules/vials prepared in syringes are acceptable.

8. 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 dried egg white 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).
2. Perform a focused physical examination, concentrating on typical target organ areas, and review vital signs.
   - The main target organ areas for an allergic response include the skin, oropharynx, upper and lower respiratory, gastrointestinal, and cardiovascular systems.
   - Pay special attention to the subject's overall appearance and demeanor, as early signals of anaphylaxis frequently display as changes from baseline in mood, level of anxiety, or concentration. Such changes can be subtle, especially in children who may not possess adequate verbal skills to describe their psychological distress.
3. Progress to the next 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 as appropriate) 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 the symptoms meet the criteria for dose-limiting symptoms and must not be involved in the preparation of the challenge doses. During the exit DBPCFC, the subject will be assessed by a physician who is not involved directly in the oversight of study treatment procedures for the subject. Ideally, the same blinded assessor will assess symptoms for the subject during the screening and exit DBPCFCs.

Suggested guidelines for the assessment of severity of specific symptoms of an allergic reaction are provided in Table 2. 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 2: Guide for Assessment of Allergic Reaction Symptom Severity by Organ System

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

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

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

Severe symptoms: All severe 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 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 serious symptoms. In this situation, safety is paramount. Certainty about the outcome must be weighed against the risk to the subject. In the event of mild symptoms,

the determination of tolerability and progression to the next dose in the DBPCFC must be based on clinical judgment.

The following general guidelines may help determine whether a dose associated with the emergence of a mild allergy 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. In this case:

- Close observation is mandatory.
- Measure vital signs (blood pressure, heart rate) 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) at least every 15 minutes until symptoms resolve, then 30 and 60 minutes after symptoms resolve, then hourly until releasing the subject.
3. Monitor oxygen saturation level by pulse oximetry if laryngeal, lower respiratory, or cardiovascular symptoms are present. Consider monitoring oxygen saturation level in all subjects, especially if the symptoms are not resolving.
4. Follow these guidelines for further observation based on symptom severity:
   - For severe symptoms, observe the subject for a minimum of 3 hours after the symptoms resolve, either at the study site or an emergency facility, as appropriate. Consider extended overnight observation if symptoms are protracted.
   - For moderate symptoms, observe the subject for a minimum of 2 hours after the symptoms resolve and longer if necessary.
   - For mild symptoms, observe the subject for a minimum of 2 hours or for 1 hour after the symptoms resolve, whichever is longer.
5. Do not release a subject with symptoms or with abnormal vital signs if changed from baseline. As appropriate, arrange for continued observation at the study site, an emergency facility, or an extended-stay (inpatient) unit. Record signs and symptoms that changed from baseline in the subject's source documents.
6. Generally, if the emergence of allergy symptoms halts the 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.

POST-DBPCFC INSTRUCTIONS AND FOLLOW-UP

Before releasing the subject, study site staff should inform the subject or 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 raw or undercooked hen eggs or food known to include raw or undercooked hen eggs. Subjects should not change their consumption of baked egg (ie, if consuming baked egg before the DBPCFC then continue consumption and if avoiding baked egg then continue to avoid).
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: Open Baked Whole Egg Food Challenge Procedures

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

The open baked whole egg food challenge conducted under this protocol will follow procedures consistent with the Practical Allergy (PRACTALL) guidelines for safety, assessment and scoring (Sampson, 2012). The open baked whole egg food challenge will use the dosing schedule shown in Table 1. Details on preparing the food challenge material and other food challenge procedures are provided in the study manual.

Table 1: Screening and Exit Open Baked Whole Egg Food Challenge Doses

Timing	Approximate Amount of Muffin [1]	Approximate Baked Egg Protein Dose (mg)	Approximate Cumulative Baked Egg Protein Dose (mg)
Screening/Exit	1/16	125	125
Screening/Exit	1/8	250	375
Screening/Exit	1/4	500	875
Screening/Exit	1/4	500	1375
Screening/Exit	1/3 (remainder of muffin)	625	2000 [1]

[1] One muffin contains approximately one-third of one whole egg, which is equivalent to approximately 2000 mg egg protein.

PROCEDURES

General Safety Considerations

A study physician will supervise all open baked whole egg food challenges.

Personnel involved in an open baked whole egg food challenge 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, beta-adrenergic agonists, and intravenous (IV) fluids.

PREPARATION FOR THE OPEN BAKED WHOLE EGG FOOD CHALLENGE

Before the Day of the Open Baked Whole Egg Food Challenge

Contact the subject and parent/caregiver: When scheduling the open baked whole egg food challenge, study site staff should allow 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. Study site staff will contact the subject or parent/caregiver in advance of the scheduled open baked whole egg food challenge to communicate the following:

- Review the events of the day (eg, study procedures, modality of the open baked whole egg food challenge, 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 open baked whole egg food challenge will be rescheduled in case of illness or symptoms such as wheezing, fever, vomiting, and diarrhea; the subject or parent/caregiver is to notify the study site if such symptoms develop before the open baked whole egg food challenge.
- 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 open baked whole egg food challenge assessment for 5 half-lives of the medication before the open baked whole egg food challenge 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 open baked whole egg food challenge.
- Instruct that the dose of study product is to be withheld on the days of the exit open baked whole egg food challenge.
- Inform that female subjects of childbearing potential will have a urine pregnancy test before starting the open baked whole egg food challenge on the day of the open baked whole egg food challenge.

On the Day of the Open Baked Whole Egg Food Challenge

1. Check the protocol schedule of activities and complete any required procedures as specified before starting the open baked whole egg food challenge.
2. Confirm the following:
   - Subject has not received study product.
   - Negative urine pregnancy test for all female subjects of childbearing potential.

- No recent or active illnesses. Reschedule the open baked whole egg food challenge if the subject is experiencing symptoms of an acute infection (eg, fever, recent nausea, vomiting, diarrhea) or any other illness that may interfere with the subject's safety or interpretation of the results. Do not conduct the open baked whole egg food challenge if illness is suspected.
- Control of chronic atopic diseases. Do not proceed with the open baked whole egg food challenge if the subject is experiencing unstable or exacerbated atopic disease such as asthma, atopic dermatitis, urticaria, or allergic rhinitis. Reschedule the open baked whole egg food challenge 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 open baked whole egg food challenge for 5 half-lives of the medication before the challenge day.

3. Measure baseline vital signs (blood pressure, heart rate, temperature).
4. Perform a focused physical examination to confirm adequate baseline. The examination should be sufficient to determine changes from baseline if signs or symptoms of an allergic reaction develop during the open baked whole egg food challenge.
5. Obtain peak expiratory flow rate (PEF) measurement.
   - For subject aged ≥ 6 years, make 3 attempts and document them in the subject's source documents. The PEF must be at the subject's baseline value (based on the screening values) or at least 80% of the predicted value, assuming the value is obtained accurately with good effort. Reschedule the open baked whole egg food challenge if the PEF does not meet one of these criteria or the investigator assesses the respiratory status as compromised.
   - For subject aged 4 to 5 years, attempt to measure PEF and document it in the subject's source documents (if unable to successfully obtain, record attempts and investigator assessment).
6. Place a saline lock if directed by the supervising physician for subjects considered at high risk of allergic reaction or severe reaction based on medical history.
7. Ensure rescue medications and resuscitation equipment are available and readily accessible, including epinephrine, diphenhydramine (oral, IV), cetirizine (oral), albuterol (nebulizer or as a metered dose inhaler), IV supplies and fluids, oxygen, and suction.
   - Calculate appropriate weight-based doses of emergency medications in advance for treatment of reactions.
   - Prepare an appropriate dose of epinephrine at a 1:1000 effective concentration for intramuscular use and have it readily accessible. An epinephrine auto-injector or epinephrine in ampules/vials prepared in syringes are acceptable.

PREPARATION OF OPEN BAKED WHOLE EGG FOOD CHALLENGE MATERIAL

Details for preparation of the food challenge material are provided in the study manual.

DOSING AND MONITORING DURING THE OPEN BAKED WHOLE EGG FOOD CHALLENGE PROCEDURE

Before Each Dose of the Open Baked Whole Egg Food Challenge

1. Measure and record vital signs (blood pressure, heart rate).
2. Perform a focused physical examination, concentrating on typical target organ areas, and review vital signs.
   - The main target organ areas for an allergic response include the skin, oropharynx, and upper and lower respiratory, gastrointestinal, and cardiovascular systems.
   - Pay special attention to the subject's overall appearance and demeanor, as early signals of anaphylaxis frequently display as changes from baseline in mood, level of anxiety, or concentration. Such changes can be subtle, especially in children who may not possess adequate verbal skills to describe their psychological distress.
3. Progress to the next 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 as appropriate) is willing.

Signs and Symptoms During the Open Baked Whole Egg Food Challenge

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 the symptoms meet the criteria for dose-limiting symptoms. Suggested guidelines for the assessment of severity of specific symptoms of an allergic reaction are provided in Table 2. 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 2: Guide for Assessment of Allergic Reaction Symptom Severity by Organ System

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

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

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

Severe symptoms: All severe symptoms are dose-limiting and indicate that the current dose level of the open baked whole egg food challenge is positive.

- **Stop the open baked whole egg food challenge, immediately initiate appropriate treatment, and closely monitor the subject**.

Moderate symptoms: Moderate symptoms are considered dose-limiting with rare exceptions, and indicate that the current dose level of the open baked whole egg food challenge is positive.

- **Stop the open baked whole egg food challenge, immediately initiate appropriate treatment, and closely monitor the subject**.

Mild symptoms: It may be difficult to predict whether mild symptoms will resolve or progress to more serious symptoms. In this situation, safety is paramount. Certainty about the outcome must be weighed against the risk to the subject. In the event of mild symptoms, the determination of tolerability and progression to the next dose in the open baked whole egg food challenge 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 open baked whole egg food challenge and initiate appropriate treatment**.

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

- Close observation is mandatory.
- Measure vital signs (blood pressure, heart rate) 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 open baked whole egg food challenge due to subjective symptoms or if the subject refuses to proceed (eg, due to significant anxiety) even if no objective allergy symptoms are documented.

OPEN BAKED WHOLE EGG FOOD CHALLENGE OUTCOMES AND TREATMENT / OBSERVATION

Negative Open Baked Whole Egg Food Challenge

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

Positive Open Baked Whole Egg Food Challenge

Treatment of subjects with symptoms: Treat subjects with any symptoms elicited by the open baked whole egg food challenge per the accepted medical practices at the study site.

Record all treatments administered for allergic reactions during an open baked whole egg food challenge 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) at least every 15 minutes until symptoms resolve, then 30 and 60 minutes after symptoms resolve, then hourly until releasing the subject.
3. Monitor oxygen saturation level by pulse oximetry if laryngeal, lower respiratory, or cardiovascular symptoms are present. Consider monitoring oxygen saturation level in all subjects, especially if the symptoms are not resolving.
4. Follow these guidelines for further observation based on symptom severity:
   - For severe symptoms, observe the subject for a minimum of 3 hours after the symptoms resolve, either at the study site or an emergency facility, as appropriate. Consider extended overnight observation if symptoms are protracted.
   - For moderate symptoms, observe the subject for a minimum of 2 hours after the symptoms resolve and longer if necessary.
   - For mild symptoms, observe the subject for a minimum of 2 hours or for 1 hour after the symptoms resolve, whichever is longer.
5. Do not release a subject with symptoms or with abnormal vital signs if changed from baseline. As appropriate, arrange for continued observation at the study site, an emergency facility, or an extended-stay (inpatient) unit. Record signs and symptoms that changed from baseline in the subject's source documents.
6. Generally, if the emergence of allergy symptoms halts the open baked whole egg food challenge, 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 open baked whole egg food challenge is halted (eg, due to anxiety or refusal to continue) and symptoms are mild and not considered to be dose-limiting.

POST-OPEN BAKED WHOLE EGG FOOD CHALLENGE INSTRUCTIONS AND FOLLOW-UP

Before releasing the subject, study site staff should inform the subject or 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 raw or undercooked hen eggs or food known to include raw or undercooked hen eggs. Subjects who tolerate the open baked whole egg food challenge without any dose-limiting symptoms will be instructed to introduce baked egg into their diet after screening per the Mount Sinai guidelines (Lieberman, 2012), or to continue their consumption of baked egg if consuming baked egg before the exit DBPCFC. Subjects who have dose-limiting allergy symptoms during the open baked whole egg food challenge will be instructed to avoid all forms of hen egg.
6. Schedule a follow-up study appointment according to the protocol.
7. Telephone the following day to inquire about post-open baked whole egg food challenge adverse events, and assist accordingly.

REFERENCES

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

Appendix 3: 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) and 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 screening open baked whole egg food challenge before remote procedures are implemented may return to the study site to complete the double-blind, placebo-controlled food challenge (DBPCFC) per protocol and enroll in the study if eligible. However, continued participation in the study will be per investigator and subject or parent/caregiver decision, based on the ability to attend study site visits and understanding the potential impact of the restrictions on study conduct.

2.2 Informed Consent

Study site personnel must obtain consent and assent (where required) before any remote 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
- Peak expiratory flow (PEF) at investigator discretion
  - Protocol-required spirometry and PEF should be performed per local clinical practice guidelines during the restrictions. Precautions should be followed per clinical recommendations to decrease risks associated with aerosol generation and possible infectious spread. PEF may be done at home at investigator discretion if routine spirometry and/or PEF cannot be done at the study site due to the restrictions.
- Pregnancy review
  - In the absence of a pregnancy test, oral confirmation must be obtained that a female subject of childbearing potential is not pregnant. Subjects will be reminded to continue to use contraception and to notify the study site if concerned about pregnancy. A pregnancy test will be performed at the next study site visit.

Procedures that will not be completed during remote study visits are as follows:

- Weight, height, and vital signs measurements
- Questionnaires to assess atopic disease
  - Asthma Control Test (ACT)/Childhood-ACT (C-ACT)
  - Eczema Area and Severity Index (EASI)
  - Total Nasal Symptom Score (TNSS)
- Quality of life questionnaires
- Physical examinations
- Skin prick tests
- Blood sample collection
- Pregnancy tests
- 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 subject or 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 subject, 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. Subjects will be

encouraged to return 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.

Subjects or 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, subjects or 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, subjects or 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.

Subjects or 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 subjects or 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.

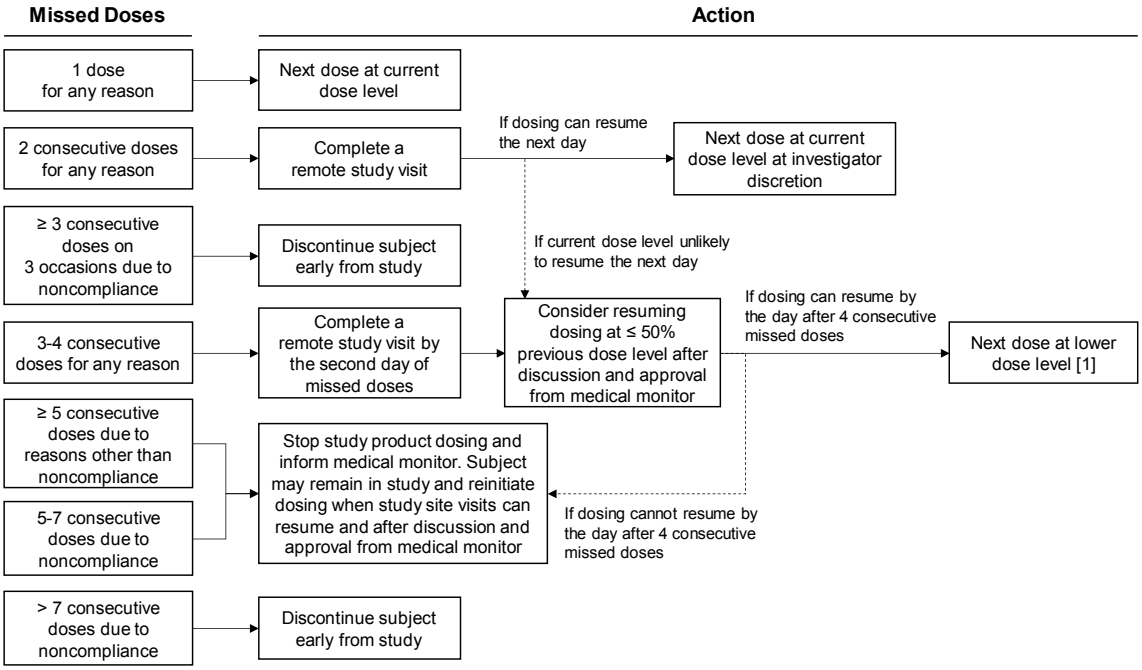
The decision to reduce a dose level when a study site visit is not possible requires discussion and approval from the medical monitor and should occur as soon as possible to ensure timely dispensation of the study product. The reduced dose level will continue until study site visits resume and dose re-escalation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

4.2 Missed Doses

Subjects or 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.

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 if applicable).
Informed consent, subject ID number	Obtain consent (and assent if applicable) before performing any study-specific procedures. Ensure consent is on current version of form reviewed by the ethics committee.
Demographics, medical history	Includes allergy history (including anaphylactic reactions) and symptoms, and diet/food allergen history.
Weight, height	
Vital signs	Measure blood pressure, heart rate, and temperature.
ACT/C-ACT, EASI, TNSS	For subject with asthma: ACT for subject aged ≥ 12 years; C-ACT for subject aged 4-11 years and parent/caregiver. For subject with eczema or atopic dermatitis: EASI. For subject with allergic rhinitis: TNSS (short form).
FAQLQ, FAIM	
PEF and/or spirometry	For subject aged ≥ 6 years, obtain PEF; record the best result of 3 attempts. For subject aged ≥ 6 years with asthma, obtain spirometry; record the best result of 3 attempts (if unable to successfully obtain, record attempts and investigator assessment). For subject aged 4-5 years, obtain PEF; record results (if unable to successfully obtain, record attempts and investigator assessment). Reliable performance is not required for study eligibility at the discretion of the investigator.
Asthma evaluation	For subject with asthma. Evaluate asthma severity per NHLBI 2007 criteria.
Food allergy instruction	Provide food/egg 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 egg) per standard of care at the study site. Verify that subject has an epinephrine auto-injector, including appropriate dose and expiry. Instruct subject to avoid eating raw or undercooked hen eggs or food known to include raw or undercooked hen eggs during the study. Document the discussion in the subject's source records.
Physical examination	Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
Pretreatment adverse event review	Record adverse event information (including allergy symptoms) from the time of signed informed consent/assent.
Concomitant medications review & instruction	Record all medications taken within 90 days before screening. Instruct subject to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction 5 half-lives of the medication before the skin prick test and randomization. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.
Skin prick test	Measure mean wheal diameter for egg white, histamines, saline, and aeroallergens.

Activity	Comments
Laboratory Evaluations (Central)	Refer to the laboratory manual for sample collection and processing.
Hematology, immunology	Complete blood count with differential. Total IgE, egg white-specific and egg white component IgE; and egg white-specific IgG4.
Optional blood sample for potential future studies	At certain study sites only. Collect before the screening open baked whole egg food challenge.
Serum pregnancy test	For all females of childbearing potential.
Food Challenges and Eligibility Confirmation	
Open baked whole egg food challenge	Measure vital signs and assess signs/symptoms of allergic reaction just before each challenge dose, and at 15-20 minutes postdose if the dosing interval between challenge doses is prolonged.
DBPCFC	Perform within 14 days after the screening open baked whole egg food challenge. Consider waiting at least 2 days before conducting the first day of the screening DBPCFC if the open baked whole egg food challenge is positive, especially if rescue medications are given (eg, steroids). If circumstances create a safety risk (eg, an intercurrent illness), the first day of the DBPCFC may be delayed after discussion with the medical monitor. 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 15-20 minutes postdose if the dosing interval between challenge doses is prolonged.
Eligibility confirmation	Confirm eligibility after completion of all screening activities.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; DBPCFC, double-blind, placebo-controlled food challenge; EASI, Eczema Area and Severity Index; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; ID, identification; Ig, immunoglobulin; NHLBI, National Heart, Lung, and Blood Institute; PEF, peak expiratory flow; TNSS, Total Nasal Symptom Score.

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

Study Period	Initial Dose Esc		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	na	na	q4w × 12w	Varies	Varies
Window (Days)	na	na	±3	±3	±3	±3	na	±3
Randomization	X							
General Activities								
Weight, height	X	X	X	X	X	X	X	X
Vital signs (blood pressure, heart rate, temperature)	X	X	X	X	X	X	X	X
ACT/C-ACT, EASI, TNSS (if completed at screening)				X	X		X (opt)	X
FAQLQ, FAIM [5]								X
PEF [6]	X	X	X	X	X	X	X (opt)	X
Symptom-directed physical examination [7]		X	X			X	X	
Complete physical examination [7]	X			X	X		X (opt)	X
Diet/food allergen exposure review	X	X	X	X	X	X	X	X
Food allergy instruction [8]	X	X	X	X	X	X	X (opt)	X
Contraception review	X	X	X	X	X	X	X (opt)	
Adverse events review [9]	X	X	X	X	X	X	X	X
Concomitant medications review & instruction [10]	X	X	X	X	X	X	X	X
Study product administration [11]	X	X	X	X	X	X	X (opt)	
Study product dispensing [12]		X	X	X	X	X	X (opt)	
Study product accountability			X	X	X	X	X (opt)	X
Telephone call [13]		X	X	X	X	X	X (opt)	X
Skin prick test to egg white, histamines, saline					X			X [14]
DBPCFC [15]								X
Open baked whole egg food challenge [16]								X
Laboratory Evaluations [17]								
Hematology, immunology [18]					X		X (opt)	X [14]

Study Period	Initial Dose Esc		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	na	na	q4w × 12w	Varies	Varies
Window (Days)	na	na	±3	±3	±3	±3	na	±3
Optional blood sample for potential future studies (certain study sites only)					X			X [14]
Urine pregnancy test [19]				X	X		X (opt)	X

[1] Day 1 activities must begin within 42 days after obtaining signed consent/assent 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 after discussion with the medical monitor if unexpected circumstances (eg, an intercurrent illness) create a safety risk.

[3] Anytime necessary to assess or follow up adverse events, at the subject's request, 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 the exit DBPCFC and open baked whole egg food challenge.

[5] Complete before the exit DBPCFC begins (on the first day only) and after the open baked whole egg food challenge.

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

[7] 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).

[8] Instruct subject to avoid eating raw or undercooked hen eggs or food known to contain raw or undercooked hen eggs during the study. Provide food/egg allergy education (including recognition of an allergic reaction, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to egg) per standard of care at the study site. Instruct subject who tolerates the screening open baked whole egg food challenge without dose-limiting allergy symptoms to include baked egg in their diet per Mount Sinai baked egg guidelines. Instruct subject who has dose-limiting symptoms during the open baked whole egg food challenge to avoid all forms of hen egg during the study.

[9] Include review of symptoms recorded in subject diary. For subject with GI adverse events of interest, instruct subject aged ≥ 8 years and parent/caregiver of subject aged 4-18 years to complete the PEESS v2.0 questionnaire while the 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.

[10] Review medications since previous visit. Instruct subject 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, the exit DBPCFC, and exit open baked whole egg food challenge. Review the prescribing information to determine the half-life of each medication for the subject's relevant age group.

[11] Administer study product at the study site per the dose modification guidelines. Measure blood pressure and heart rate and assess signs/symptoms of allergic reaction at 15-30 minutes postdose and approximately every 30 minutes thereafter (until 90 minutes postdose or end of observations for symptoms, whichever is last).

[12] 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 and open baked whole egg food challenge.

[13] Contact subject or parent/caregiver by telephone on the day after initial dose-escalation day 2, up-dosing visits, maintenance visits, exit DBPCFC, and open baked whole egg food challenge for adverse events review and to inquire about compliance with study product dosing. Remind the subject or parent/caregiver to record symptoms in the diary (except after the exit open baked whole egg food challenge).

[14] Perform/collect before the exit DBPCFC (on the first day only).

[15] Subject must tolerate the 300 mg daily dose for approximately 2 consecutive weeks before having the exit DBPCFC. Conduct on 2 separate days within 7 days.

[16] Conduct within 14 days after the second day of the exit DBPCFC. If circumstances create a safety risk (eg, an intercurrent illness), the open baked whole egg food challenge may be delayed after discussion with the medical monitor.

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

[18] Complete blood count with differential. Total IgE, egg white-specific and egg white component IgE, and egg white-specific IgG4.

[19] For all females of childbearing potential.

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; DBPCFC, double-blind, placebo-controlled food challenge; EASI, Eczema Area and Severity Index; ED, early discontinuation; Esc, escalation; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; GI, gastrointestinal; Ig, immunoglobulin; na, not applicable; opt, optional; PEESS v2.0, Pediatric Eosinophilic Esophagitis Symptom Scores version 2; PEF, peak expiratory flow; q, every; TNSS, Total Nasal Symptom Score; Unsch, unscheduled; w, weeks.

Appendix 6: Study Schedule of Activities for Subjects Who Discontinue Treatment Early, Exit With Ongoing Adverse Event, or Have Gastrointestinal Adverse Events of Interest: 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 for ongoing adverse events is for 30 days or until consent for follow-up is withdrawn. Safety follow-up for ongoing serious adverse events is for 30 days or until the ongoing serious 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 results, pathology results], if applicable) is monthly for the duration of safety follow-up (Section 5.5.1).

[3] For adverse events ongoing at early discontinuation or study exit. Telephone subject or 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 subject aged ≥ 8 years and parent/caregiver of subject aged 4-18 years 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.