CLINICAL STUDY PROTOCOL

ARC001
Oral Desensitization to Peanut in Peanut-Allergic Children and Adults Using Characterized Peanut Allergen (CPNA) Oral Immunotherapy (OIT)

Protocol Amendment 3 – 14 May 2014
Reference Numbers: NCT01987817, EudraCT 2021-002087-47

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CLINICAL STUDY PROTOCOL

Protocol Title:	Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Oral Immunotherapy (OIT)
Investigational Drug:	Characterized Peanut Allergen (CPNA)
Protocol Number:	ARC001
IND Number:	IND 15463
Sponsor:	Allergen Research Corporation (ARC) 2000 Alameda de las Pulgas, Suite 161 San Mateo, CA 94403 USA
Version:	Amendment 3
Date:	14 May 2014

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from Allergen Research Corporation, unless it is necessary to obtain informed consent from potential study subjects.

CLINICAL STUDY PROTOCOL ARC001
Sponsor Personnel

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Chief Medical Officer	Robert Elfont MD, PhD ARC

CLINICAL STUDY PROTOCOL ARC001
Clinical Research Organization (CRO) Personnel

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Sponsor Protocol Approval

Protocol ARC001	Version/Date: Amendment 3/ 14 May 2014
Sponsor: Allergen Research Corporation (ARC)	
Short Title: CPNA Peanut OIT	

I have read protocol ARC001, and I approve it. I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

_____ _____

Chief Medical Officer (Print) Date

_____ _____

Chief Executive Officer (Signature) Date

Principal Investigator Protocol Approval

Protocol ARC001	Version/Date: Amendment 3/ 14 May 2014
IND: 15463	Principal Investigator:
Short Title: CPNA Peanut OIT	

I have read protocol ARC001, and I approve it. As the Principal Investigator, I agree to conduct this protocol according to Good Clinical Practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance" *(April 1996), and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, state and federal requirements.*

_____ _____

Principal Investigator (Print) Date

_____ _____

Principal Investigator (Signature) Date

Synopsis

Protocol ARC001 Synopsis	
Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT)**
Short Title	CPNA Peanut OIT
Clinical Phase	2
IND	15463
IND Sponsor	Allergen Research Corporation (ARC)
Number of Subjects	Approximately 50 peanut allergic subjects will be randomized 1:1 to peanut Oral Immunotherapy (OIT) versus placebo.
Objective	The primary objective is to demonstrate the efficacy of Characterized Peanut Allergen through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children and young adults (ages 4-26 years, inclusive). The secondary objectives are: • To demonstrate the safety of Characterized Peanut Allergen as measured by incidence of adverse events and dosing symptoms. • To evaluate the immunological effects of peanut OIT therapy. • To determine the time course of tolerated up-dosing • To evaluate safety based on physician global assessment of disease activity
Study Design	This is a multicenter, randomized, double-blind placebo-controlled study of efficacy and safety of characterized peanut OIT in peanut allergic individuals. The study will consist of a screening period, a double-blind OIT treatment (up-dosing and maintenance) period, followed by a double-blind, placebo controlled food challenge (DBPCFC). An open-label safety follow-up study (ARC002) is planned after completion of ARC001. All eligible subjects will receive an escalating dose of either characterized peanut allergen or placebo. Beginning at Week 22, eligible subjects who reach the targeted daily dose of 300 mg/day and maintain that dose for 2 weeks will undergo a DBPCFC. Subjects who have not reached 300 mg/day will continue to up-dose as tolerated until they are eligible for the DBPCFC (after 2 weeks home dosing with 300 mg/day) or until they reach Week 34, at which time they will be considered an escalation failure. A DBPCFC will be performed for those subjects achieving the target dose of 300 mg and continuing to receive that dose for 2 weeks. Each subject will be unblinded when he/she completes the DBPCFC at the end of 2 weeks treatment with 300 mg/day. All placebo subjects are eligible for rollover into the ARC002 protocol. Placebo subjects in ARC002 will undergo an escalation schedule identical to that for active subjects in the ARC001 protocol. All subjects on active treatment who pass the DBPCFC are eligible to proceed to ARC002. Those who do not pass will be considered endpoint failures. A Data Monitoring Committee (DMC) has been established for the study to monitor the study for safety.
Study Duration	6 to 9 months

Protocol ARC001 Synopsis	
Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT)**
Primary Endpoint	The primary clinical efficacy endpoint is the proportion of subjects who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC
Secondary Endpoints	• Change from baseline in tolerated dose of peanut protein at DBPCFC • Maximum dose achieved with no or mild symptoms at exit DBPCFC • Physician global assessment: Disease activity as measured on a 100 mm visual analogue scale (VAS) • Changes in peanut-specific IgE and IgG4, changes in skin prick test (SPT) mean wheal diameters • The safety of peanut OIT based on dosing symptoms and reported adverse events (AEs) including serious adverse events (SAEs)
Study Product and Design	Characterized Peanut Allergen (CPNA) or placebo. Doses characterized and normalized for total protein and specific peanut allergen ratios will ascend per the dosing regimen outlined below. Study product will be provided in break-apart capsules formulated to contain 0.5, 1.0, 10, and 100 mg of peanut protein. Matching placebo capsules identical to the active capsules will be used to maintain double-blinded conditions. An unblinded clinical site pharmacist will dispense the study products to the investigational site in a manner consistent with the current dose level and treatment assignment without breaking the blind for the subjects and the other study personnel.
Inclusion Criteria	• Age 4 through 26 years • Clinical history of allergy to peanuts or peanut-containing foods • Serum IgE to peanut of > 0.35 kU_A/L [determined by UniCAP™ within the past 12 months] and/or a SPT to peanut > 3 mm compared to control • Experience dose-limiting symptoms at or before the 100 mg dose of peanut protein (measured as 200 mg of peanut flour) on screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines • Written informed consent from adult subjects • Written informed consent from parent/guardian for minor subjects • Written assent from minor subjects as appropriate (ie, above the age of 7 years) • Use of birth control by female subjects of child-bearing potential • Should not be residing in the same address as another subject in this study • Cannot have participated in a clinical trial 30 days prior to randomization
Exclusion Criteria	• History of cardiovascular disease • History of frequent or repeated, severe or life-threatening episodes of anaphylaxis or anaphylactic shock

Protocol ARC001 Synopsis	
Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT)**
	• History of other chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (e.g., heart disease, diabetes) • History of eosinophilic gastrointestinal disease • Current participation in any other interventional study • Subject is on 'build-up phase" of immunotherapy to another allergen (i.e., has not reached maintenance dosing) • Severe asthma (2007 NHLBI Criteria Steps 5 or 6, see **Appendix 2**) • Mild or moderate (2007 NHLBI Criteria Steps 1-4) asthma, if uncontrolled as defined by any of the following: ➢ Forced expiratory volume in 1 second (FEV1) < 80% of predicted, or FEV1/FVC < 75%, with or without controller medications (only for age 6 or greater and able to do spirometry) or ➢ Inhaled corticosteroid (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICSs based on National Heart, Lung, and Blood Institute [NHLBI] dosing chart) or ➢ 1 hospitalization in the past year for asthma or ➢ Emergency Room (ER) visit within 6 months • History of steroid medication use (via intravenous [IV], intramuscular [IM] or oral administration) in any of the following manners: ➢ daily oral steroid dosing for >1 month during the past year *or* ➢ burst or steroid course in the past 3 months *or* ➢ >2 burst oral steroid courses in the past year ≥1 week in duration • Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing or DBPCFC • Lack of an available palatable vehicle food to which the subject is not allergic • Use of omalizumab within the past 6 months, or current use of other investigational forms of allergen immunotherapy (eg, oral or sublingual) or immunomodulator therapy (not including corticosteroids) • Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers • Pregnancy or lactation • Having the same place of residence as another subject in the study • Participation in another clinical trial within 30 days prior to randomization

Protocol ARC001 Synopsis	
Title	**Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT)**
Treatment Description	Screening/baseline: All eligible subjects will undergo a DBPCFC of up to 100 mg (143 mg cumulative) peanut protein or placebo during the screening portion of the study. The screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines using up to 100 mg (143 mg cumulative) peanut protein or placebo. Additionally, the DBPCFC will progress through the dose levels in an unaltered sequence without repeating any dose. Those subjects who have dose-limiting symptoms at or before the 100 mg (143 mg cumulative) dose of peanut protein (measured as 200 mg of peanut flour) will be randomized 1:1 to active treatment or placebo. Up-dosing OIT treatment: Subjects will receive daily oral dosing of peanut or placebo OIT for about 6 to 9 months. All escalation doses (see escalation table below) will occur in a clinical research center or other monitored setting. All up-dosing will be performed under direct observation. Therapy details are found in **Section 3** and **Section 6** of the protocol. Exit DBPCFC: After the subjects have been up-dosed to a 300 mg/day dose and have continued to receive that dose for at least 2 weeks, subjects will undergo a DBPCFC of up to 600 mg (1043 mg cumulative) peanut protein or placebo. All placebo subjects are eligible for rollover into the ARC002 protocol. Placebo subjects in ARC002 will undergo an escalation schedule identical to that for active subjects in the ARC001 protocol. All subjects on active treatment who pass the DBPCFC in ARC001 will be eligible for the ARC002 study.
Study Procedures	The following procedures will be performed according to the scheduled visits tabulated in **Appendix 1**: • Informed consent • Inclusion/exclusion criteria • Medical/Allergy history • Concomitant medications • Physical exam, including height and weight • Vital signs (BP, PR, temperature) • Spirometry (FEV1) and/or Peak Expiratory Flow Rate (PEFR) • Pregnancy test • Diet history • Blood draw for peanut specific IgE and IgG4 • Optional blood draw (pre-DBPCFC and 5-10 days post-DBPCFC) for exploratory analyses by the Immune Tolerance Network (ITN) • Skin prick test (SPT) • Clinical research center drug administration • Dispensing of study drugs for home dosing/Return of unused drugs • Dose assessment to decide for maintenance or up-dosing • Peak Expiratory Flow Rate (PFER) prior to any DBPCFC • Abbreviated double-blind, placebo controlled food challenge (DBPCFC) per PRACTALL guidelines • Physician Global Assessment of Disease Activity • Monitoring for dosing compliance and symptoms • Adverse event (AE) monitoring

Protocol ARC001 Synopsis		
Initial Days 1 to 3 (Visit 01) Escalation Schedule		
Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Cumulative Study Product Dose (mg peanut protein or placebo)**
1	0.5	0.5
2	1.0	1.5
3	1.5	3.0
4	3.0	6.0
5	6.0	12

Doses will be delivered at 20 to 30 minute intervals.

Subjects who are unable to tolerate a dose of 3.0 mg at the end of Day 1 will be considered an initial day escalation failure.

All subjects who tolerate a dose of at least 3 mg on Day 1 will return on Day 2 to receive their maximum tolerated dose (3 mg or 6 mg) under direct observation.

Subjects with either no symptoms or mild symptoms on Day 2 at either 3 mg or 6 mg may start daily dosing at their highest tolerated level, and will not be required to return for Day 3.

Subjects who experience moderate or severe symptoms after receiving a 6 mg dose on Day 2 will return on Day 3 to receive the next lower dose (3 mg) under direct observation.

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

Future dose escalations will occur every 2 weeks with the initial dose increase administered in the clinical research center.

Escalation Dosing			
Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Interval (weeks)**	**% Increase**
6	12	2	
7	20	2	67%
8	40	2	100%
9	80	2	100%
10	120	2	50%
11	160	2	33%
12	200	2	25%
13	240	2	20%
14	300	2	25%

Capsules are opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.

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Glossary of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme inhibitors
AE	Adverse Event
Ag	Antigen
ARB	Angiotensin-receptor blockers
ARC	Allergen Research Corporation
BP	Blood Pressure
CFR	US Code of Federal Regulations
CoFAR	Consortium of Food Allergy Research
CPNA	Characterized Peanut Allergen
CRC	Clinical Research Center
CRF	Case Report Form
CTC	Common Toxicity Criteria
DBPCFCs	Double-Blind, Placebo-Controlled Food Challenges
DMC	Data Monitoring Committee
EC	Exposure Challenge
ELISA	Enzyme-linked immunosorbent assays
EoE	Eosinophilic Esophagitis
ER	Emergency Room
FDA	US Food and Drug Administration
FEV1	Forced Expiratory Volume
GCP / cGCP	Good Clinical Practice / Current Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid(s)
IFNg	Interferon Gamma
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITN	Immune Tolerance Network
IV	Intravenous
kU_A/L	Kilounits of Antibody per Liter

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes for Health
OIT	Oral Immunotherapy
PEFR	Peak Expiratory Flow Rate
PI	Principal Investigator
PR	Pulse Rate
PRACTALL	PRACtical issues in ALLergology Joint United States/European Union Initiative
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SLIT	Sublingual Immunotherapy
SPT	Skin Prick Test
SUSAR	Suspected /Unexpected Serious Adverse Reaction
Th1	T Helper 1
Th2	T Helper 2
TLR	Toll-like Receptor
Tr1	T Regulatory 1
Tregs	Regulatory T cells
VAS	Visual Analogue Scale
WHO	World Health Organization

1. Background and Rationale

1.1 Background

Peanut allergy is a common and serious condition that disproportionately affects children, and is commonly associated with severe reactions, including life-threatening anaphylaxis. The current standard of care in management of food allergy is dietary avoidance of the food, and education of the subject/family in the acute management of an allergic reaction. The burden of avoidance and constant fear of accidental exposure negatively affects the health-related quality of life for both subjects and their families.[1,2,3]

Currently, the only treatment for peanut allergy is a peanut-free diet and ready access to self-injectable epinephrine. However, strict avoidance diets can be complicated due to difficulty in interpreting food labels[4] and by the presence of undeclared or hidden allergens in commercially prepared foods.[5,6] Accidental ingestions are unfortunately common, with up to 50% of food-allergic patients having at least one allergic reaction over a two-year period.[7]

Allergic reactions to peanut can be severe and life-threatening; and peanut and/or tree nut allergies account for the vast majority of fatal food-induced anaphylaxis.[8] This combination of strict avoidance diets, the high incidence of accidental exposures, and the risk of severe or even fatal reactions with accidental exposures adds a tremendous burden and stress on patients and their families.

Specific immunotherapy for food allergy, in particular for peanut allergy, in the forms of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT), has been studied in recent years and has demonstrated encouraging safety and efficacy results in early clinical trials, including beneficial immunologic changes.[9-18] There is evidence that OIT may induce desensitization in most subjects, with immunologic changes over time indicating progression toward clinical tolerance.[15,19-22]

The goal of this program is to induce a state of desensitization to peanut protein defined as the absence of moderate or severe reaction following ingestion of a specific dose of peanut protein. This state of desensitization should be sufficient to protect a subject with peanut allergy from an accidental exposure to a small amount of peanut protein while maintaining a peanut restricted diet. Protection to a whole peanut, approximately 250 mg of peanut protein (measured as 500 mg of peanut flour), would afford a meaningful level of clinical protection against accidental exposure to peanut protein, since accidental exposures are typically to only small amounts of the allergen.[23]

1.2 Peanut OIT

Varshney et al[15] conducted a double-blind placebo controlled study of an OIT protocol in subjects with severe allergy to peanut protein and consistently demonstrated an increase in the dose of allergen tolerated by the subjects versus baseline with a good safety profile.

In addition, peanut OIT has been administered under IND (Investigational New Drug Application) at Duke and Arkansas and under a separate IND at Stanford.* A total of 44 cases from Duke/Arkansas were analyzed and 14 cases from Stanford. Efficacy was demonstrated in 26 cases (17 active and 9 placebo) matching the published information. Sixteen out of 17 active subjects were escalated to a dose between 2400 and 4000 mg over a year. Oral food challenge results were significantly better for the active treatment group than the placebo group where both groups tolerated a mean of 12 mg of peanut protein at baseline, while at one year the mean for the active treatment group was 5000mg of protein and for the placebo group 280 mg of peanut protein ($P < 0.001$ by Wilcoxon rank-sum test).[15]

Dosing symptoms were typical for OIT protocols including rash, wheezing, rhinorrhea, sneezing, itching, abdominal pain, nausea, vomiting, and diarrhea. Symptoms were noted in both the active treatment and the placebo group. Of the 39 cases on active treatment, 4 doses of epinephrine were administered – 2 during dosing and 2 during double-blind, placebo controlled food challenges (DBPCFCs). The Stanford data reported on 14 subjects who were dosed with peanut OIT and dosing symptoms severity and rate were similar to those reported in the Duke/Arkansas data.

These published findings, along with the additional clinical data, are the basis for a Phase II trial to investigate peanut OIT for efficacy and safety in desensitizing peanut allergic subjects. Protocol ARC001 is designed to be a double-blinded, placebo-controlled study establishing the efficacy of CPNA for conducting oral immunotherapy. Protocol ARC002 and any additional follow-on studies will be related but separate open-label protocols designed to demonstrate the safety of daily dosing with CPNA for an extended period (months to years), to confirm unblinded the efficacy of OIT with CPNA at a dose of 300 mg/d of peanut protein in the former ARC001 placebo population, to provide an option to explore unblinded the safety and tolerability of OIT, and to maintain any desensitization that may have been achieved by subjects.

1.3 Rationale for Selection of Study Population

The study will enroll approximately 50 subjects from 4 to 26 years of age with a history of allergy to peanuts or peanut-containing foods. All subjects enrolled must undergo an initial DBPCFC to peanut that must be positive at or before the 100 mg (143 mg cumulative) dosing level of peanut protein (measured as 200 mg of peanut flour with 50% protein content) in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) consensus guidelines,[24] regardless of how they were initially diagnosed as peanut allergic. This will enroll subjects who are sensitive to peanut exposure and expected to benefit from desensitization to the equivalent of a whole peanut, and corresponds to a specific level of allergen exposure

* Data, provided courtesy of Wesley Burks of the University of North Carolina (formerly of Duke University Medical Center), Stacie Jones of University of Arkansas for Medical Sciences, and Kari Nadeau of Stanford University School of Medicine, on file at Allergen Research Corporation and summarized in a report, "Study Report for Clinical Trial Data Collected Under IND for Peanut Oral Immunotherapy," prepared by a third-party vendor, The EMMES Corporation (Rockville, MD).

conducted during the enrollment oral food challenge. The patients generally most severely affected by ingestion of peanut allergen are very young children; however, young children have limited ability to reliably follow a study protocol. Thus, 4 years of age was selected as the lower cutoff age for this study.[25] The upper age limit of 26 years was selected to insure that the subjects do not have underlying concomitant conditions that could preclude the use of epinephrine in subjects exposed to the risk of anaphylaxis.

1.4 Rationale for Selection of Study Drug Regimen

The rationale for dosing builds on the work of the Consortium of Food Allergy Research (CoFAR) and its investigators. The dosing consists of a single-day initial escalation at very low doses, followed by a build-up phase of dose escalation, with a single escalation occurring every 2 weeks. This has been demonstrated to be well tolerated and efficacious in previous studies and will be used in this current trial.[26]

1.5 Rationale for the Dose Used for the DBPCFC

The study DBPCFC will be conducted in accordance with the recommended PRACTALL guidelines although the screening DBPCFC will not exceed the 100 mg (143 mg cumulative) dose to assess inclusion criteria, and the exit DBPCFC will not go above a 600 mg (1043 mg cumulative) dose to help ensure patient safety. Additionally, the DBPCFCs will progress through the dose levels in an unaltered sequence without repeating any dose.

The exit DBPCFC will assess protection against slightly more than 1 peanut's worth of peanut protein 300 mg (≥443 mg cumulative dose) since accidental exposures typically occur to limited amounts of allergen. To assess further desensitization, patients tolerating the 300 mg (443 mg cumulative) incremental dose will also be challenged with 600 mg (1043 mg cumulative), although not up to the 3000 mg dose (4443 mg cumulative), since at this point they will have been up-dosed only to the 300 mg dose level.

Since subjects are enrolled only if they are sensitive to ≤100 mg level (143 mg cumulative) peanut protein on the screening DBPCFC, this would represent a 10x increase in the incremental dose tolerated (and 10.3x increase in cumulative dose) which would be in line with the previous demonstration of a 10x total increase, although this was after treatment for 1 year, and to larger amounts of peanut protein. A DBPCFC started at a very low dose is conducted to confirm that spontaneous desensitization has not occurred.

1.6 Known and Potential Risks and Benefits to Human Participants

1.6.1 Risks

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

In subjects with peanut allergy, there have been many oral immunotherapy studies performed using procedures and dosing similar to those proposed in this Phase 2 study.

In general, safety profile has been very good across the studies, and based on those studies, approximately 80%, 15%, and <1% of the subjects are expected to have a mild, moderate or severe symptoms, respectively, during some point in their dosing with the peanut immunotherapy. It is important to note that essentially all adverse events have been allergy-related, predictable, and reversible. The major atypical adverse event from peanut OIT that has been reported in the literature is a single case of eosinophilic esophagitis, reversible upon stopping dosing.

Specifically, the buildup and daily maintenance doses of peanut OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing, and/or shortness of breath in addition to severe anaphylaxis. The likelihood of a subject experiencing any allergic symptoms is expected to be lessened by initiating dosing at extremely small amounts of characterized peanut allergen and by buildup of dosing under observation in a clinical setting until the maintenance dose is achieved.

Oral food challenges may induce an allergic response. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects have an allergic reaction during the challenges, they may need oral, intramuscular, or intravenous medications, and will be treated per study center standard of care. Trained personnel, including a physician, as well as medications and equipment (per PRACTALL recommendations and investigational site standard operating procedures), will be immediately available to treat any reaction. The anticipated rate of serious life-threatening anaphylactic reactions would be < 0.1%.

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

1.6.2 Benefits

There is no guarantee that participation in this study will help the subject. The subject may receive placebo during the double-blind treatment period of the study. Information from this study may help researchers to better understand peanut allergy or to develop future tests or treatments to help patients with this condition.

2. Objectives

2.1 Primary Objective

The primary objective is to demonstrate the efficacy of Characterized Peanut Allergen through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children and young adults (ages 4-26 years, inclusive).

2.2 Secondary Objective(s)

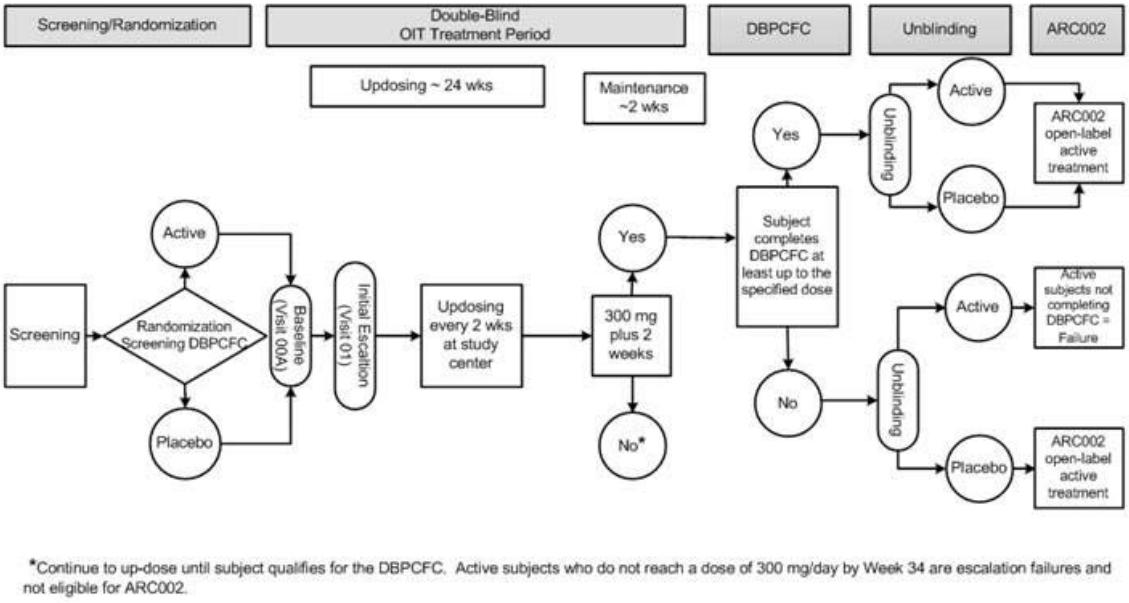
The secondary objectives are:

- To demonstrate the safety of Characterized Peanut Allergen as measured by incidence of adverse events and dosing symptoms.
- To evaluate the immunological effects of peanut OIT therapy.
- To determine the time course of tolerated up-dosing
- To evaluate safety based on physician global assessment of disease activity

3. Study Design

ARC001 is a multi-center, randomized, double-blind placebo-controlled study. The study design is illustrated in **Figure 3–1.**

Figure 3–1. Study Design



*Continue to up-dose until subject qualifies for the DBPCFC. Active subjects who do not reach a dose of 300 mg/day by Week 34 are escalation failures and not eligible for ARC002.

3.1 Screening period

Subjects age 4 to 26 years with a clinical history of peanut allergy, a serum IgE to peanut of ≥ 0.35 kU_A/L and/or a skin prick test (SPT) to peanut of ≥3 mm versus control will be screened. All eligible subjects will undergo an initial DBPCFC at screening. The DBPCFC will include both a peanut challenge and a placebo challenge. The screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines using up to 100 mg (143 mg cumulative) peanut protein and placebo.

Those who have dose-limiting symptoms at or before the 100 mg (143 mg cumulative) dose of peanut protein (measured as 200 mg of peanut flour) will be enrolled into the study, since they would be expected to benefit from protection against limited amounts of allergen exposure. Those who successfully consume a dose of >100 mg or more of peanut protein during the screening DBPCFC will be considered to be screen failures and will not be randomized.

Any subject who is assessed to have had dose-limiting symptoms to both parts of the screening DBPCFC (i.e., to oat flour as well as peanut flour) will be considered to be a screen failure and will not be randomized.

Approximately 50 subjects who pass screening will be randomized 1:1 to either active peanut protein or placebo using TEMPO™'s password-protected Interactive Web Response System (IWRS) provided by Clinipace Worldwide.

3.2 Treatment period

The treatment build-up phase will start with an initial escalation at the study center, followed by up-dosing for approximately 24 weeks. The treatments will be conducted in a double-blind fashion. An unblinded clinical site pharmacist will prepare the study medications at different doses according to each subject's treatment assignment. The subjects and the rest of the study personnel will be blinded to the treatment assignments.

After the initial escalation visit (comprising 2 or 3 days), subjects will report to the study center every 2 weeks to escalate their OIT dose, up to an expected daily dose of 300 mg/day of peanut protein in subjects able to tolerate the up-dosing. The dosing escalation schedule is described in detail in **Table 3-1** and **Table 3-2**.

Table 3-1. Initial Dosing Schedule for Peanut OIT

Initial Days 1 to 3 (Visit 01) Escalation Schedule		
Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Cumulative Study Product Dose (mg peanut protein or placebo)**
1	0.5	0.5
2	1.0	1.5
3	1.5	3.0
4	3.0	6.0
5	6.0	12
Doses will be delivered at 20 to 30 minute intervals. Subjects who are unable to tolerate a dose of 3.0 mg at the end of Day 1 will be considered an initial day escalation failure. All subjects who tolerate a dose of at least 3 mg on Day 1 will return on Day 2 to receive their maximum tolerated dose (3 mg or 6 mg) under direct observation. Subjects with either no symptoms or mild symptoms on Day 2 at either 3 mg or 6 mg may start daily dosing at their highest tolerated level, and will not be required to return for Day 3. Subjects who experience moderate or severe symptoms after receiving a 6 mg dose on Day 2 will return on Day 3 to receive the next lower dose (3 mg) under direct observation. Subjects with moderate or severe symptoms at 3 mg on either Day 2 or Day 3 will be considered escalation failures. Future dose escalations will occur every 2 weeks with the initial dose increase administered in the Clinical Research Center.		

Table 3-2. Escalation Dosing Schedule for Peanut OIT

Escalation Dosing			
Dose #	**Study Product Dose (mg peanut protein/day or placebo)**	**Interval (weeks)**	**% Increase**
6	12	2	
7	20	2	67%
8	40	2	100%
9	80	2	100%
10	120	2	50%
11	160	2	33%
12	200	2	25%
13	240	2	20%
14	300	2	25%
Capsules are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly.			

All subjects who reach and tolerate 300 mg/day for 2 weeks will undergo an exit DBPCFC. Those unable to achieve a dose of 300 mg/day of peanut protein by 34 weeks will be considered escalation failures and will not undergo an exit DBPCFC.

During the treatment period, the subjects will be monitored for tolerability as illustrated in **Figure 6–1** and **Figure 6–2** (see **Section 6.8.4**).

If a subject is removed from therapy because of failing escalation during the initial escalation period (Visit 1; Days 1 to 3), the subject will be followed for safety and asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

If a subject's up-dosing is halted because of failing subsequent build-up (i.e., after the initial escalation period; Visit 1), the subject will continue to be dosed at the last tolerated dose level and to be followed for safety biweekly (following their established visit schedule) until Week 24, i.e., a maintenance phase (See also Section 6.8.4). Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5).**

For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be followed for safety and asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

For subjects who achieve the targeted dose of 300 mg/d by Week 34, the maintenance phase comprises the last two weeks of the study.

Subjects who prematurely discontinue treatment before Week 24 for any reason will be brought in for an early discontinuation visit 14 days after their last dose.

A Data Monitoring Committee (DMC) has been established and will meet every 3 months to monitor the study for safety.

3.3 Exit DBPCFC

All subjects who reach the targeted daily dose of 300 mg/day and maintain that dose for 2 weeks will undergo an exit DBPCFC. The exit DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in an unaltered sequence (**Table 6-2**), without repeating any dose.

Each subject will be unblinded after he/she completes the DBPCFC.

Subjects who do not reach the target dose by Week 34 are not eligible for the exit DBPCFC, and will be considered escalation failures. They will be unblinded no sooner than Week 24.

All placebo subjects are eligible for rollover into ARC002. Placebo subjects enrolled in ARC002 will undergo an escalation schedule identical to that for active subjects in the ARC001 protocol. All subjects on active treatment who pass the DBPCFC are eligible to proceed to ARC002. Subjects in the active treatment group who do not pass the DBPCFC at the 300 mg (443 mg cumulative) protein level will be considered endpoint failures and will not be eligible for rollover into the ARC002 protocol.

3.4 Follow-up Study ARC002

All placebo subjects are eligible for rollover into ARC002. Placebo subjects enrolled in ARC002 will undergo an escalation schedule identical to that for active subjects in the ARC001 protocol. All subjects on active treatment who successfully complete the ARC001 DBPCFC are eligible to proceed to ARC002 and continue dosing, with an opportunity for additional up-dosing.

3.5 Study Design Safety Considerations

The study design considers important safety issues:

- All dose escalations will be supervised in the clinic
- The peanut OIT will only escalate to a maximum 6 mg single dose during the initial escalation on Day 1
- Dosing symptoms and adverse events will be captured throughout the study
- All subjects and/or their participating family (as appropriate for age and home circumstances) will be provided with an epinephrine auto-injector and will be trained in its use
- Subjects will be strongly cautioned against consuming any peanuts or peanut-containing foods other than the study product while on study, and will be instructed to remain on a peanut-free diet.

3.6 Primary Efficacy Endpoint

The primary clinical efficacy endpoint is the proportion of subjects in each group who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC.

3.7 Secondary Endpoints

The secondary endpoints are as follows:

- Change from baseline in tolerated dose of peanut protein at DBPCFC
- Maximum dose achieved with no or mild symptoms at exit DBPCFC
- Physician global assessment: Disease activity as measured on a 100-mm visual analogue scale (VAS)
- Changes in peanut-specific IgE and IgG4, changes in SPT mean wheal diameters.

- The safety of peanut OIT as measured through dosing symptoms, adverse events (AEs), and serious adverse events (SAEs).

4. Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

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

1. Age 4 through 26 years
2. Clinical history of allergy to peanuts or peanut-containing foods
3. Serum IgE to peanut of $\geq$ 0.35 kU_A/L [determined by the UniCAP™ automated immunoassay system within the past 12 months] and/or a SPT to peanut > 3mm compared to control
4. Experience dose-limiting symptoms at or before the 100 mg (143 mg cumulative) dose of peanut protein (measured as 200 mg of peanut flour) or on screening DBPCFC conducted in accordance with PRACTALL guidelines
5. Written informed consent from parent/guardian for minor subjects
6. Written assent from minor subjects as appropriate (e.g., above the age of 7 years)
7. Use of birth control by female subjects of child-bearing potential
8. Should not be residing in the same address as another subject in this study
9. Cannot have participated in a clinical trial 30 days prior to randomization

4.2 Exclusion Criteria

Subjects who meet any of these criteria are not eligible for enrollment as study subjects:

1. History of cardiovascular disease
2. History of frequent or repeated, severe or life-threatening episodes of anaphylaxis or anaphylactic shock
3. History of other chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (e.g., heart disease, diabetes)
4. History of eosinophilic gastrointestinal disease
5. Current participation in any other interventional study
6. Subject is on 'build-up phase" of immunotherapy for another allergen (i.e., has not reached maintenance dosing)
7. Severe asthma (2007 NHLBI Criteria Steps 5 or 6, see **Appendix 2**)
8. Mild or moderate (2007 NHLBI Criteria Steps 1-4) asthma, if uncontrolled as defined by any of the following:
   - FEV_1 < 80% of predicted, or FEV1/FVC < 75%, with or without controller medications (only for age 6 or greater and able to do spirometry[†]) or

[†] Spirometry is to be attempted in all subjects ≥ 6 years of age. For subjects ages 6-11 years: if valid spirometry results are not successfully obtained, the attempt is to be documented. Measures of peak flow will be acceptable for the entry criteria if results are > 80% of predicted. For subjects 4 or 5 years of age, peak flow rates are to be attempted but reliable performance is not required for the subject to enter the study. The attempt must be documented, and a clinical assessment is required.

- ICS dosing of > 500 mcg daily fluticasone (or equivalent inhaled corticosteroids based on NHLBI dosing chart) or
- 1 hospitalization in the past year for asthma or
- ER visit within six months

9. Use of steroid medications (IV, IM or oral) in the following manners:
   - history of daily oral steroid dosing for >1 month during the past year or
   - burst or steroid course in the past 3 months prior to inclusion or
   - >2 burst oral steroid course in the past year of at least one week duration
10. Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing or DBPCFC
11. Lack of an available palatable vehicle food to which the subject is not allergic
12. Use of omalizumab within the past six months, or current use of other investigational forms of allergen immunotherapy (e.g., oral or sublingual) or immunomodulator therapy (not including corticosteroids)
13. Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers
14. Pregnancy or lactation
15. Having the same place of residence as another subject in the study
16. Participation in another clinical trial within 30 days prior to randomization

4.3 Premature Subject Termination from the Study

4.3.1 Criteria

No subject randomized into this trial who discontinues treatment for any reason will be replaced.

Unless required for safety reasons (i.e., medical treatment of SAEs), subjects eligible for an exit DBPCFC will not be unblinded earlier than their scheduled DBPCFC. Subjects who are considered escalation failures will be unblinded no sooner than Week 24.

Any subject may be prematurely terminated from additional allergen exposures for the following reasons:

1. Life-threatening symptoms (CoFAR Grade 4; refer to **Table A4-3** in **Appendix 4**), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
2. Severe symptoms (CoFAR Grade 3; refer to **Table A4-3** in **Appendix 4**), including, but not limited to, those that require aggressive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) or those that are recurrent
3. Poor control or persistent activation of secondary atopic disease (e.g., atopic dermatitis, asthma)
4. Started on ARBs, ACE, beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing doctor

5. Pregnancy
6. Circumstances (e.g., concurrent illness, such as gastroenteritis) requiring missed peanut OIT maintenance dosing of > 7 consecutive days
7. Non-adherence with home peanut OIT dosing protocol (excessive missed days; i.e., > 3 consecutive days missed on 3 or more occasions) would be a safety issue warranting discontinuation

Any subject may also be prematurely terminated from the study if:

8. The subject elects to withdraw consent from all future study activities, including follow-up.
9. The subject is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the subject have failed).
10. The subject develops biopsy-documented eosinophilic esophagitis (EoE).
11. The subject's continued participation in the study is assessed by the investigator to constitute a threat to the safety of the subject or the safe conduct of the study
12. The subject dies (CoFAR Grade 5)

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

4.3.2 Follow-up of Subjects Who Discontinue Treatment Only

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

5. Study Medication

5.1 Formulation, Packaging and Labeling

The active study product is characterized peanut allergen in the form of peanut flour formulated with a bulking agent and a flow agent in pre-measured graduated doses comprising capsules containing 0.5, 1.0, 10 and 100 mg each of peanut protein, with an HPLC fingerprint and specific ELISAs performed against key allergenic proteins to demonstrate stability and lot-to-lot comparability. Placebos, containing excipients only, will be provided as matching capsules which are identical to the active capsules.

All study products (both peanut allergen and placebos) will be packaged and labeled at the central manufacturer. The products will then be shipped to a drug depot where they will be labeled and inventoried for shipment to the clinical sites. Study products will be shipped by the drug depot to the site pharmacist for distribution to the site study personnel. The unblinded clinical site pharmacist will dispense study products to the

investigational site in a manner consistent with the current dose level and treatment assignment without breaking the blind for the subjects and the other study personnel.

All study products will be stored in a secure location and kept refrigerated between 2°C and 8°C.

5.2 Preparation, Administration and Dosage

The pre-packaged study product will be provided from the site pharmacy in appropriate doses to deliver the specified dose as outlined in **Section 3**. The capsules should be drawn apart, and gently rolled between finger and thumb, followed by a light tap to ensure full delivery of contents. The contents of the capsules will be mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other age-appropriate food. The food may not be heated before consumption, and must also be one to which the subject is not additionally allergic. The product must be consumed promptly after mixing. If there is a delay of more than 24 h in consumption, the product will be discarded and a new product dose mixed and consumed. Every attempt will be made to administer the dose of study product at the same time of day. A target interval of at least 12 h should pass between doses.

Active and placebo capsules are identical in appearance but there are slight differences between the colors (from off-white to beige) of the contents of the capsule depending on the dose. The unblinded pharmacist will prepare the capsules according to the needed dose per subject, and will not transmit the treatment assignment to the study investigator or study staff. The subjects or supervising adult will mix the provided capsule contents with the vehicle food.

At each clinic visit, each subject will receive a set of capsules to be taken at home according to their specific dose level while maintaining treatment blinding. The subjects should be instructed to document capsules taken at home using diary logs and bring all unused capsules back to the clinic at every visit.

5.3 Drug Accountability

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

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

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

5.4 Assessment of Compliance with Study Treatment and Monitoring

Families will document daily dosing and any reaction to at-home dosing by diary logs. Central monitoring of compliance will be performed. Families will be provided with 24-h emergency contact information from each site.

All unused study medication should be brought back to the clinic with each visit for reconciliation of remaining capsules.

5.5 Modification of Study Treatment

As described in the protocol (**Section 6.8**), peanut OIT doses may be adjusted by the study physician if the subject is unable to tolerate the scheduled dose increase. If such a dose modification occurs, the subject will return all unused capsules of study medication during the dose adjustment visit, and be dispensed capsules at the adjusted dose level.

5.6 Concomitant Medications

Except as indicate in **Section 5.9**, all subjects may continue their usual medications, including those taken for asthma, allergic rhinitis and atopic dermatitis, during the study. However, they must be able to discontinue antihistamines 5 half-lives prior to the initial day of escalation, skin testing and oral food challenges. Usual topical steroid use is permitted at the time of skin testing.

5.7 Prophylactic Medications

None

5.8 Rescue Medications

Treatment of individual allergic reactions during peanut OIT therapy should be with either an antihistamine and/or epinephrine, along with IV fluids, albuterol, oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely to already have an epinephrine auto-injection device, but for those who do not, an epinephrine auto-injection device will be provided. Subjects and parents will be trained in proper use and will be able to demonstrate proper technique with the epinephrine auto-injection device.

5.9 Prohibited Medications

1. Omalizumab (Xolair)
2. Systemic (oral) corticosteroids used for any greater duration than a total of 3 weeks consecutive weeks throughout the study. If used, subjects must not be up-dosed during the 3 days after ceasing the administration of oral steroids
3. Beta-blockers (oral)
4. Angiotensin-converting enzyme (ACE) inhibitors
5. Angiotensin-receptor blockers (ARB)
6. Calcium channel blockers

6. Study Procedures

6.1 Enrollment and Randomization

Subjects will have an initial screening DBPCFC consisting of both a peanut challenge and a placebo challenge before randomization. The peanut and placebo challenges will be conducted in a double-blind fashion, using study products provided by the unblinded site pharmacist or nutritionist. Those reacting to ≤100 mg of peanut protein (143 mg cumulative) will be randomized in a 1:1 ratio to peanut OIT or placebo. Those able to successfully consume >100 mg of peanut protein during their DBPCFC will not be eligible for the study. Randomization will be done via TEMPO™. If accrual capacity is adequate, each of the expected 8 sites should enroll approximately 6-8 subjects each. Because of the requirement for the peanut DBPCFC, the screening and baseline visits may be conducted in more than 1 day.

The study procedures are tabulated in **Appendix 1** and are listed per visit below.

6.2 Screening Visit (Visit 00)

The screening visits which may occur over several days (Visit 00) will include the following procedures:

- Informed consent and assent
- Inclusion/exclusion criteria
- Medical and allergy history
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- Spirometry (FEV1) and/or Peak Expiratory Flow Rate (PEFR) prior to any DBPCFC; 3 attempts of FEV1 are performed and the best value is taken; 3 attempts of PEFR are to be performed, and the best value taken. PEFR should be measured at the same time for each visit assessment.
- Serum pregnancy test, for females of childbearing potential
- Diet history
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic assay), the amount to be specified by local laboratory guidelines
- Optional blood draw (pre-DBPCFC and 5-10 days post-DBPCFC) for exploratory analysis by the Immune Tolerance Network (ITN). The amount taken should be 5 mL/kg in children weighing ≥30 kg, with a maximum of 60 mL in total.
- Skin prick test to peanut extract
- An initial double-blind DBPCFC conducted in accordance with PRACTALL guidelines as described in **Section 6.6**.

6.3 Baseline Visit

Subjects who meet eligibility criteria will return for a baseline visit. This visit will include the following procedures and will take place over several days:

- Repeat review of informed consent
- Review of inclusion/exclusion criteria
- Medical and allergy history
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- Spirometry (FEV1) and/or PEFR prior to any DBPCFC; 3 attempts of FEV1 are performed, and the best value is taken; 3 attempts of PEFR are to be performed, and the best value taken. PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Optional blood draw (pre- and 5-10 days post-DBPCFC) for exploratory analysis by ITN. The amount taken should be 5 mL/kg in children weighing ≥30 kg, with a maximum of 60 mL in total. Blood draw should be completed per National Institutes for Health (NIH) guidelines.
- Physician global assessment of disease activity using a 100-mm VAS

6.4 Study Treatment Visits

6.4.1 Initial Escalation Days 1 to 3 (Visit 01)

The following assessments will be performed at Visit 01 at the Clinical Research Center:

Day 1 Initial Escalation

- OIT administration of peanut protein or matching placebo on escalation day (Visit 01) with dosing beginning at 0.5 mg ,with graduated doses up to 6.0 mg (if tolerated). Subjects at the end of Day 1 tolerating less than 3.0 mg single dose will be considered an initial day escalation failure. The schedule for initial day dose escalation is shown in **Table 3-1**.
- Concomitant medications
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.

- Diet history
- Monitoring for allergic symptoms (see **Section 6.8**)
- Adverse events monitoring

Subjects may have clear liquids or JELL-O during the day of the initial day escalation protocol while they are being given the desensitization doses.

If symptoms occur which prevent escalation to 6.0 mg, the highest tolerated dose (at least 3.0 mg) will be accepted as the "desensitization" dose for further escalation (see **Figure 6**–1 in **Section 6.8.4**). The maximum tolerated dose on Day 1 (e.g., 3.0 or 6.0 mg) will be given on Day 2 as a single dose under medical observation at the Clinical Research Center. If moderate symptoms occur on Day 2, the subject will return to the Clinical Research Center on Day 3 for the next lower dose (must be at least 3.0 mg) under direct observation. If symptoms prevent initial escalation desensitization dosing to 3.0 mg, the subject will be dropped from study treatment due to escalation failure and followed longitudinally for safety. These subjects will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

A physician will be available at all times during any of the Clinical Research Center peanut OIT dosing visits.

Day 2 Initial Escalation
All subjects will return to the clinic on Day 2 for their next dose. This dose will be the previous day's dose or the last tolerated dose from the initial day escalation. The maximum dose is 6.0 mg. The minimum dose for Day 2 is 3.0 mg.

Those subjects administered: 3.0 mg
- If tolerated, return home on that dose for 2 weeks until the next escalation
- If not tolerated, the subject is considered an escalation failure, discontinued from treatment, and followed for safety until the Early Discontinuation Visit

Those subjects administered: 6.0 mg
- If tolerated, return home on that dose for 2 weeks until next escalation
- If not tolerated, return on Day 3 with a 1-step reduction (3.0 mg)

Day 3 Initial Escalation
Those subjects with moderate symptoms on Day 2 at the 6.0 mg dose will return on Day 3 for an observed dose. The maximum dose on Day 3 would be 3.0 mg.
Those subjects administered 3.0 mg
- If tolerated, return home on that dose for 2 weeks until next escalation.
- If not tolerated, the subject is considered an escalation failure, discontinued from treatment, and followed for safety until the Early Discontinuation Visit.

5 to 10 days post-DBPCFC

- Optional post DBPCFC blood draw for exploratory analysis by ITN. The amount taken should be 5 mL/kg in children weighing ≥30 kg, with a maximum of 60 mL in total. Blood draws should be completed per NIH guidelines.

6.4.2 Up-dosing/Escalation visits (Up to 34 weeks post-Visit 01)

The following procedures are scheduled for the up-dosing phase, which will last approximately 24 weeks).

- Return to clinic every 2 weeks for up-dosing up to a maximum of 300 mg daily dose. The first dose of study product will be administered at the clinic.
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until next visit
- Monitoring for compliance and allergic symptoms (phone contact 1 week after each escalation visit)
- Adverse events monitoring

Subjects should not take their daily maintenance dose on the day of the clinic visits. The initial up-dose is to be administered at the clinic.

Subjects who require dosing reduction during the 2-week period will reset their 2-week escalation schedule to maintain the new dose for a 2-week period prior to attempting to escalate again. The procedure for setting the new, lower, dose is outlined in **Section 6.8.2** and depends on the severity of the dose-related symptoms. Any dose escalation attempts may be postponed for 1-2 extra weeks based on clinical judgment. An escalation attempt must be made by 4 weeks, unless escalation is to be delayed further due to administration of epinephrine as defined in **Section 6.8**. Failure to successfully escalate for three consecutive attempts will result in the subject being considered an escalation failure and dose escalation will be halted at the last tolerated dose level. These subjects will be followed for safety biweekly (following their established visit schedule) while continuing to be dosed at their last tolerated dose level until Week 24, i.e., a maintenance phase (see also **Section 6.8.4**). Dosing will be stopped after the Week 24 visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be asked to return to the Clinical Research Center 14 days

following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

For any noted symptoms during the maintenance phase, the same study dosing rules for build-up phase will be followed. As noted above, for subjects who halt dose-escalation prior to Week 24, the maintenance phase extends to Week 24; and for subjects who halt dose-escalation after Week 24, there is no maintenance phase. For subjects who achieve a dose of 300 mg/d by Week 34, the maintenance phase comprises the last two weeks of the study.

Subjects will continue to follow a peanut restricted diet for the duration of the study.

Note that all study products to be used in the build-up phase for this study have been filled from a single lot, so no reductions based on lot changes should be necessary.

6.4.3 Visit 02 (after approx. 12 weeks post-Visit 01)

- Study product administration at clinic
- Medical/allergy history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Diet history
- Return unused capsules to the clinic at each visit
- Take home capsules for daily dosing until the next visit
- Monitoring for compliance and allergic symptoms (phone contact 1 week after each escalation visit)
- Adverse events monitoring

Subjects will continue to follow a peanut-restricted diet for the duration of the study. For any noted symptoms during the maintenance phase, the same study dosing rules for the build-up phase will be followed.

6.5 Visit 03 - Exit Visit / Early Discontinuation Visit

Subjects who tolerate 300 mg/day and are maintained at this dose for 2 weeks will return to the clinic for an Exit visit. For these subjects, the Exit visit will occur at approximately 6-9 months post-Visit 01.

Subjects who fail escalation or build-up, or who prematurely discontinue treatment, will return to the site for an Early Discontinuation visit that consists of the same procedures as the Exit visit, but without a DBPCFC or associated optional blood draws. An Early Discontinuation visit is to occur 14 days from the last dose of study product.

The following procedures will be performed at the Exit visit:

- Medical/allergy history
- Concomitant medications
- Physical exam, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Urine pregnancy test, for females of childbearing potential
- Diet history
- Blood draw for peanut-specific IgE and IgG4 measurement (mechanistic assays), the amount to be specified by local laboratory guidelines.
- Optional blood draw (pre-DBPCFC) for exploratory analysis by ITN. The amount taken should be 5 mL/kg in children weighing ≥30 kg, with a maximum of 60 mL in total. Blood draw should be collected per NIH guidelines.
- Skin prick test to peanut extract
- Physician global assessment of disease activity using a 100-mm VAS
- Monitoring for compliance and allergic symptoms

In addition to the procedures listed above, eligible subjects will have an exit DBPCFC performed. Eligible subjects are those who tolerate 300 mg/day and are maintained at this dose for 2 weeks.

For placebo subjects only:

- Exit DBPCFC conducted in accordance with PRACTALL guidelines as described in **Section 6.6.2**, then proceed to ARC002

For active-treatment subjects completing DBPCFC only:

- Proceed to ARC002

Each subject participating in the study will be unblinded when he/she completes the Exit visit procedures (including the exit DBPCFC for eligible subjects).

6.6 Double-Blind, Placebo Controlled Food Challenge (DBPCFC) in accordance with PRACTALL guidelines

The DBPCFC is performed by feeding gradually increasing amounts of the suspected food under physician observation.[25,26] A sample of food challenge from the PRACTALL guidelines using peanut flour is given in **Table 6-1.**

Table 6-1. PRACTALL DBPCFC Doses Using Peanut Flour with 50% Peanut Protein Content for Screening DBPCFC

Challenge Doses	
Peanut protein (mg)	**Peanut flour with 50% protein content (mg)**
3	6
10	20
30	60
100	200

6.6.1 Screening Double-Blind, Placebo Controlled Food Challenge (DBPCFC) – For All Subjects

The initial DBPCFC for eligibility will consist of ascending levels of the peanut flour (containing ~50% peanut protein) or placebo in gradually increasing doses at 20-30 min intervals. The DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in an unaltered sequence without repeating any dose. The procedure will also be modified in that the top dose will be capped at 100 mg (143 mg cumulative) peanut protein or placebo. The PRACTALL doses as shown in **Table 6-1** will be used, as well as PRACTALL rules for safety, assessment, scoring, and stopping. At the investigator's discretion, a 1 mg dose may be added at the beginning of the escalation (for a maximum cumulative dose of 144 mg peanut protein). In the event that the 1 mg dose is added, any rules that apply to subjects based on a cumulative dose of 143 mg will also apply to subjects based on a cumulative dose of 144 mg.

The DBPCFC is conducted as 2 challenges during a single day visit or over 2 days, using a placebo (oat flour) for one challenge and peanut (as peanut flour) for the other. If conducted in a single day, at least 3 h must separate the first half of the challenge from the second half of the challenge. The challenge is performed under double-blind conditions so that neither the subject, nor the subject's caregiver nor the physician knows which challenge contains the peanut or the placebo.

6.6.2 Exit Double-Blind, Placebo Controlled Food Challenge (DBPCFC)- For All Subjects

The exit DBPCFC will be conducted in a manner similar to the screening DBPCFC but with a dose increasing up to 600 mg (1043 mg cumulative) peanut protein as shown in **Table 6-2**.

Subjects receiving active treatment will be considered a study success if they are able to complete a challenge with 300 mg (443 mg cumulative) peanut protein.

Table 6-2. Doses Using Peanut Flour with 50% Peanut Protein Content for Exit DBPCFC

Challenge Doses	
Peanut protein (mg)	**Peanut flour with 50% protein content (mg)**
3	6
10	20
30	60
100	200
300	600
600	1200

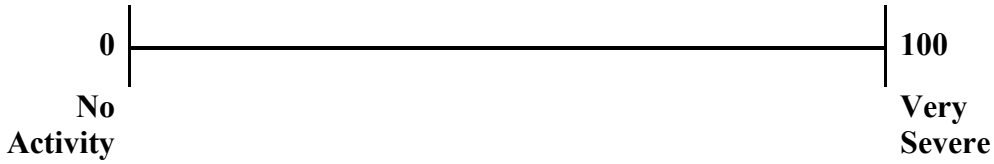
6.7 Physician Global Assessment

A 100-mm visual analog scale (VAS) will be used by the investigators to assess overall disease activity as a marker for safety.

In assessing overall disease activity, the investigator should consider the frequency of allergic reactions (both observed and reported), their type, their severity, and the dose level at which they have occurred. With these factors in mind, the investigator is to assign a single integrated overall disease activity score.

The investigators will be asked:

"*How would you rate the severity of the overall disease activity on a scale of 0, no disease activity, to 100, very severe disease activity?"*



Investigators are permitted to refer back to previous assessments when making their VAS determination of overall disease activity.

Although not validated specifically as an instrument for evaluating food allergies, the VAS is, nevertheless, a widely used tool in assessing disease activity, especially in inflammatory diseases.

6.8 Reactions and Treatment of Reactions

6.8.1 Reactions and Treatment of Reactions to Peanut OIT During Initial Escalation

The process algorithm for symptoms during the initial escalation protocol is shown in **Figure 6–1** in **Section 6.8.4.**

Subjects may develop symptoms during the initial escalation protocol, similar to those seen during other desensitization protocols (e.g., venom immunotherapy, drug desensitization). The severity of the reaction will be determined on the basis of the investigator's judgment, using the definitions in the PRACTALL consensus report on DBPCFC as a general guide. The investigator's judgment will also be required to determine the best course of action, with possible actions being the following:

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

For *oral/pharyngeal pruritus* occurring in isolation – the recommended action is to continue the normal dosing in 30 min (though the action taken is, as always, at the investigator's clinical discretion).

For *mild symptoms*, including, but not limited to:

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

Depending on the investigator's discretion, the action should be either:

- Advance to next dose in 30–60 min *or*
- Treat with antihistamine and then resume dose escalation within 60 min of last dose, if symptoms have resolved to the point where the investigator assesses the subject as safe to continue dosing (i.e., having no or minimal residual signs or symptoms)

If *moderate symptoms* occur, including, but not limited to:

- Skin – systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema
- Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea

- GI – persistent moderate abdominal pain/cramping/nausea, more than a single episode of vomiting and/or diarrhea

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

If moderate symptoms occur at any of the doses below 6 mg (i.e., up to and including 3 mg), then the desensitization protocol will be discontinued and the subject considered an escalation failure. The decision to discontinue escalation (at any dose below, or at, 3 mg) is based solely on the determination that the symptoms of allergic reaction are moderate, regardless of whether treatment is instituted or what type of treatment is instituted. If moderate symptoms occur only at the 6 mg dose, then the following day's dose (Day 2 or Day 3) will be reduced to 3 mg.

The Medical Monitor is to be available at all times to answer any questions or to assist in any decisions related to the study protocol.

If more *severe symptoms* occur, including, but not limited to:

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

The actions taken should be to discontinue the initial escalation and administer the appropriate rescue medications. The desensitization protocol will be discontinued regardless of the dose at which the severe symptom or symptoms occurred, and the subject considered an escalation failure.

Summary of Initial Escalation Dosing Requirements (see also **Figure 6–1** in **Section 6.8.4**)

In general, if the subject requires one or two doses of antihistamine treatment for mild symptoms during the initial escalation protocol, then the initial escalation may be continued. If, however, the subject requires a second medication (e.g., epinephrine, a beta-agonist, or other medications) in addition to an antihistamine, or multiple doses of antihistamines, the initial escalation is to be terminated and the subject will receive no further OIT, even if symptoms are assessed to be mild.

In the event of moderate symptoms occurring during the initial escalation, the initial escalation is to be terminated and the subject will receive no further OIT, regardless of whether treatment is instituted or what type of treatment is instituted. The only exception to this is if the occurrence of moderate symptoms is restricted to the 6 mg dose. In this case, and this case only, may testing be attempted the following day (Day 2 or Day 3) at a reduced dose (3 mg).

If the initial escalation is completed with no symptoms or only mild symptoms, subjects should have, at a minimum, a 2-h post-protocol observation period before continuing in the study. If the subject experiences moderate to severe symptoms, the observation period is to be at least 4 h, and up to 24 h (in an appropriate facility), based on the nature and severity of the symptoms and the treatment regimen required to stabilize the subject's condition.

6.8.2 Reactions During Build-up Phase: Preventative and Non-pharmacological Interventions

The process algorithm for symptoms during the build-up/up-dosing phase is shown in **Figure 6–2.**

Subjects will begin the Clinical Research Center dosing scheme as outlined until 300 mg/day of peanut protein is reached. Subjects will return for a supervised dose escalation in the clinic every 2 weeks. It is advised that subjects be called the morning of the day after each dose escalation visit to assess for delayed or biphasic allergic reactions. Subjects will be called 1 week after each dose escalation visit to assess for dosing compliance and dose reactions. Any dose escalation attempts may be postponed for 1-2 extra weeks based on clinical judgment. An escalation attempt must be made by 4 weeks. Subjects should withhold their daily home dose on the escalation day but should take all other prescribed medications. Note that the daily home dose should be taken as part of a meal. It is recommended that the dose be taken at a consistent time (within a 4-hour time period), and it is critical to take the dose every day. Doses should be separated by at least 12 h.

Subjects who require dosing reduction during the 2-week period will reset their 2-week escalation schedule to maintain the new dose for a 2-week period prior to attempting to escalate again.

With the occurrence of symptoms of a dose-reaction or any allergic reaction, subjects/parents (or guardians) are instructed to call the study site.

Should significant systemic symptoms, which may include mild symptoms based on physician discretion or moderate or greater symptoms, be reported during the daily home dosing, the symptom/dosing algorithm will be followed (see **Figure 6–2**) to determine the best course of action. The appropriate treatment will depend on the type and severity of symptoms (see **Section 6.8.3**).

If significant symptoms occur consistently following three attempts to increase the daily oral dose in the Clinical Research Center or clinic with each attempt spaced 2-4 weeks apart, dosing escalation will be halted at the last tolerated dose and the subject will be considered an escalation failure. These subjects will be followed for safety biweekly (following their established visit schedule) while continuing to be dosed at their last tolerated dose level until Week 24, i.e., a maintenance phase (See also **Section 6.8.4**). Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). No additional DBPCFC will be performed.

Subjects will be free from active wheezing or a flare of atopic dermatitis prior to any dose escalation. Subjects will be maintained on their current dose of study product until their flare of asthma or atopic dermatitis resolves.

Subjects will be cautioned against activities likely to increase reactivity (e.g., exercising or taking hot showers or baths within 4 h after dosing).

At the physician's discretion, temporary dose reductions, ranging from a 1-step decrement (i.e., to the previous dose) to approximately half of the current dose level (to the nearest feasible available whole dose), can be instituted while subjects are suffering from symptoms of an upper respiratory infection or influenza, or during menses. If the dose is reduced by more than 1 step or for more than 3 days, the subject is to return to the CRC within 7 days of the dose-reduction for dose re-escalation under direct observation. If the reduction in dose is maintained for ≤3 days, then the pre-reduction dose may be resumed directly. For dose reductions of 1 dose level maintained for ≤3 days, whether dose re-escalation is to occur at home or in the CRC is at the investigator's discretion. If the reduction in dose is maintained for >3 days, the subject will have his or her 2-week escalation schedule reset to maintain the new dose for a 2-week period prior to re-escalating in a bi-weekly stepwise fashion.

Doses may also be withheld at the investigator's discretion, in response to an AE, whether the AE is assessed to be treatment-related or not. If doses are withheld for this, or any, reason, the rules for missed peanut OIT doses (**Section 6.7**) apply.

Subjects may develop symptoms during dosing for the build-up phase. The investigator's judgment will be required to determine the best course of action with possible actions being the following:

- Continue with daily home dosing
- Continue the same daily dose for the rest of the 2-week interval, with 50% of the dose split between doses given 8-12 h apart
- Return for repeat dosing in Clinical Research Center

- Return for dosing of previously tolerated dose (without escalation) in Clinical Research Center
- Discontinuation of dosing

If a subject has a dose escalation in the Clinical Research Center without symptoms, the action should be to continue per protocol with daily home dosing of the tolerated dose with the next escalation visit to the Clinical Research Center 2 weeks later.

If the subject experiences only oral/pharyngeal pruritus during the administration of the daily dose, then the same dose can be repeated the next day at home and continued throughout the interval unless other symptoms begin to develop (see below).

For *mild symptoms*, defined as:

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

The action should be either to repeat the dose the next day (Day 2) at home or to have the subject return to the Clinical Research Center the next day (Day 2) for a repeat of the previous day's dose or the last tolerated dose (at the physician's discretion). If the dose is tolerated, then the subject will continue on that dose and return at the normal interval. If the dose causes mild symptoms again, then the subject will return to the Clinical Research Center (Day 3) and be given the last tolerated dose (i.e., a 1-step dose reduction) or a 2-step dose reduction. If tolerated, the subject will continue on this dose for the normal time interval. If mild symptoms recur, a further 1-2-step reduction should be administered the next day (Day 4) in the CRC. If tolerated then that dose should be continued for 2 weeks. If not tolerated, revert to a lower dose.

If *moderate symptoms* occur, defined as:

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

The action should be to have the subject return to the Clinical Research Center the next day (Day 2) for dosing with the previous day's dose or the last tolerated dose (at the investigator's discretion) under observation. If the dose is tolerated, the subject will continue on that daily home dose for the normal time interval per protocol. If the subject does not tolerate this dose, the subject should receive the last tolerated dose (i.e., a 1-step

dose reduction) or a 2-step dose reduction as their next day's dose (Day 3) in the Clinical Research Center. If this dose is tolerated, it will be continued as the daily home dose for the normal time interval, then escalation attempted in the Clinical Research Center as noted below. If this dose is not tolerated, then the next dose will be a further 1-2-step reduction in dosing (per investigator judgment), and the dose will be given in the Clinical Research Center (Day 4). If this next dose is not tolerated, then a discussion with the Medical Monitor will ensue to make a decision about whether to continue the subject on study-product treatment in the study.

If more *severe symptoms* occur, defined as:

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

The action should be to treat the subject, and at the physician's discretion either 1) have them return to the Clinical Research Center the next day (Day 2) for dosing with a 2-step reduction in dose under observation or 2) discontinue them from the study product treatment. If the subject tolerates the dose reduction, then they will remain on that dose for 2 weeks and then return to the Clinical Research Center for the dose escalation. A discussion with the Medical Monitor may ensue to make a decision about whether to continue the subject on study product treatment in the study.

If a subject fails dose escalation after three consecutive attempts (with 2-4 weeks between), he/she will be considered an escalation failure and the last tolerated dose will be accepted as the maintenance dose (to Week 24). If the dose escalation is completed with no symptoms, subjects should be observed for 30 min. If the subject exhibits mild symptoms, the duration of the observation period should be 1-2 h post-protocol. For moderate to severe symptoms, the observation period should be at least 4 h and up to 24 h based on symptoms and the treatment regimen needed to stabilize the subject's condition.

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

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

Any subject who discontinues build-up dosing due to repeated allergic reactions to the characterized peanut allergen will have his/her mechanistic blood draw (refer to **Section 8**) within approximately 1 week of discontinuation of therapy.

6.8.3 Treatment for Reactions During the Build-up Phase: Pharmacological and Supportive Treatments

Treatment of individual reactions should be with either an antihistamine and/or epinephrine, along with IV fluids, a beta-agonist (e.g., albuterol, by inhaler or nebulizer), oxygen, and glucocorticosteroids, as indicated. Generally, for mild symptoms requiring treatment, the subject should receive antihistamines. Generally, for moderate symptoms requiring treatment, the subjects should receive antihistamines and/or epinephrine, as indicated. If severe anaphylaxis (stage 3 anaphylaxis defined in **Appendix 3**) occurs at any time, dose escalation will stop and the dose will be reduced to the last tolerated dose and the subject continued on that dose as long-term maintenance without further escalation.

Antihistamines

If a subject receives antihistamines only, the dose escalation can be continued. If symptoms during a build-up day require antihistamines in multiple doses (>2) or in combination with other medications (except epinephrine), there should be a dose reduction by 1-2 doses with the next dose given in the CRC. If epinephrine is administered, then a different course of action is to be taken (see below). If dose escalation fails or requires treatment after two more escalation attempts, each spaced 2 to 4 weeks apart, the dose should be reduced to the last tolerated dose and continued long term (to Week 24) without further escalation. The subject will be followed for safety biweekly (following their established visit schedule) while continuing to be dosed at their last tolerated dose level until Week 24, i.e., a maintenance phase (see also **Section 6.8.4**). Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). No additional DBPCFC will be performed.

Epinephrine - General

Any reaction (in clinic or at home) that requires two or more doses of epinephrine will halt further dose escalation for this individual. Maintenance on the last tolerated dose is to be continued until Week 24. Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will

be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

Epinephrine - Clinic

If a single administration of epinephrine is required during escalation in the clinic, the dose of study medication is to be reduced by two increments, or to the last tolerated dose (at the physician's discretion), and dose escalation is to continue.

If a single administration of epinephrine is required a second consecutive time during this escalation attempt, the dose should be reduced by two doses, and the subject continued on that dose for 6-8 weeks. After 6-8 weeks at the reduced dose, an escalation attempt may be tried in clinic.

If a single administration of epinephrine is required a third consecutive time during this escalation attempt, the dose should be reduced by two doses and the subject continued on that dose as long-term maintenance (to Week 24) without further escalation. (Note: an event requiring 3 consecutive administrations of epinephrine is to be reported within 24 hours of its occurrence, see **Section 7.1** and **7.7.2**). The subject will continue to be followed for safety biweekly (following their established visit schedule) while continuing to be dosed at their last tolerated dose level until Week 24. Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). For subjects who halt dose-escalation after Week 24, there will be no maintenance phase. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**). No additional DBPCFC will be performed.

Epinephrine - Home

If a single administration of epinephrine use occurs during dosing at home, this epinephrine use is not counted as one of the uses described above, unless severe anaphylaxis is assessed to have occurred at home. The subject should return to clinic for an observed dose prior to resuming any dosing at home.

6.8.4 Reactions During Maintenance Phase

This phase consists of the subject receiving the maximum achieved daily dose of peanut OIT.

Subjects who fail escalation during the initial escalation period (Visit 1; Days 1 to 3), i.e., subjects who do not tolerate a minimum of 3 mg of study product (CPNA or matching placebo), will stop dosing and will not enter a maintenance phase. These subjects will be followed for safety and be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see, **Section 6.5**).

Subjects whose up-dosing is halted because of failing subsequent build-up (i.e., after the initial escalation period; Visit 1), will continue to be dosed at the last tolerated dose level and to be followed for safety biweekly (following their established visit schedule) until Week 24. The length of time from the cessation of up-dosing to Week 24 will constitute the maintenance phase for these subjects. The maintenance phase, thus, may vary in length from subject to subject. Dosing will be stopped after the Week 24 Visit; and the subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see, **Section 6.5**).

There will be no maintenance phase for subjects who halt dose-escalation after Week 24. Dosing in these subjects will be discontinued when dose-escalation is stopped. They will be followed for safety and asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

Subjects who achieve the targeted dose of 300 mg/d by Week 34 will then enter a 2-week maintenance phase. For these subjects, the maintenance phase will be followed by a DBPCFC performed at their Exit Visit (no later than week 36; see, **Section 6.5**).

All subjects will continue to follow a peanut-restricted diet for the duration of the study.

For any noted symptoms during the maintenance phase, the **same** study dosing rules for the build-up phase will be followed.

Figure 6–1. Schematic for Initial (Visit 01) Day Escalation

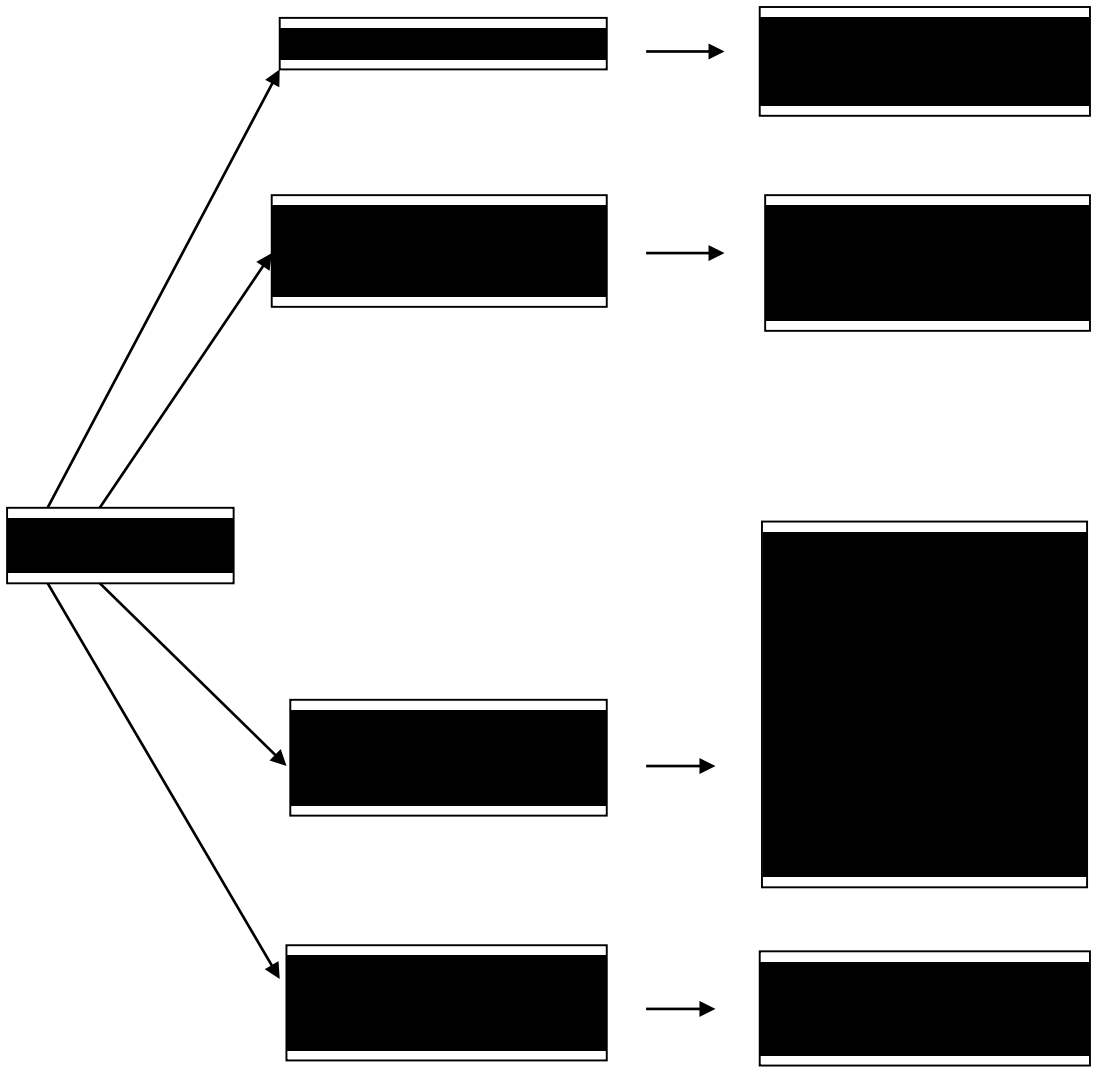
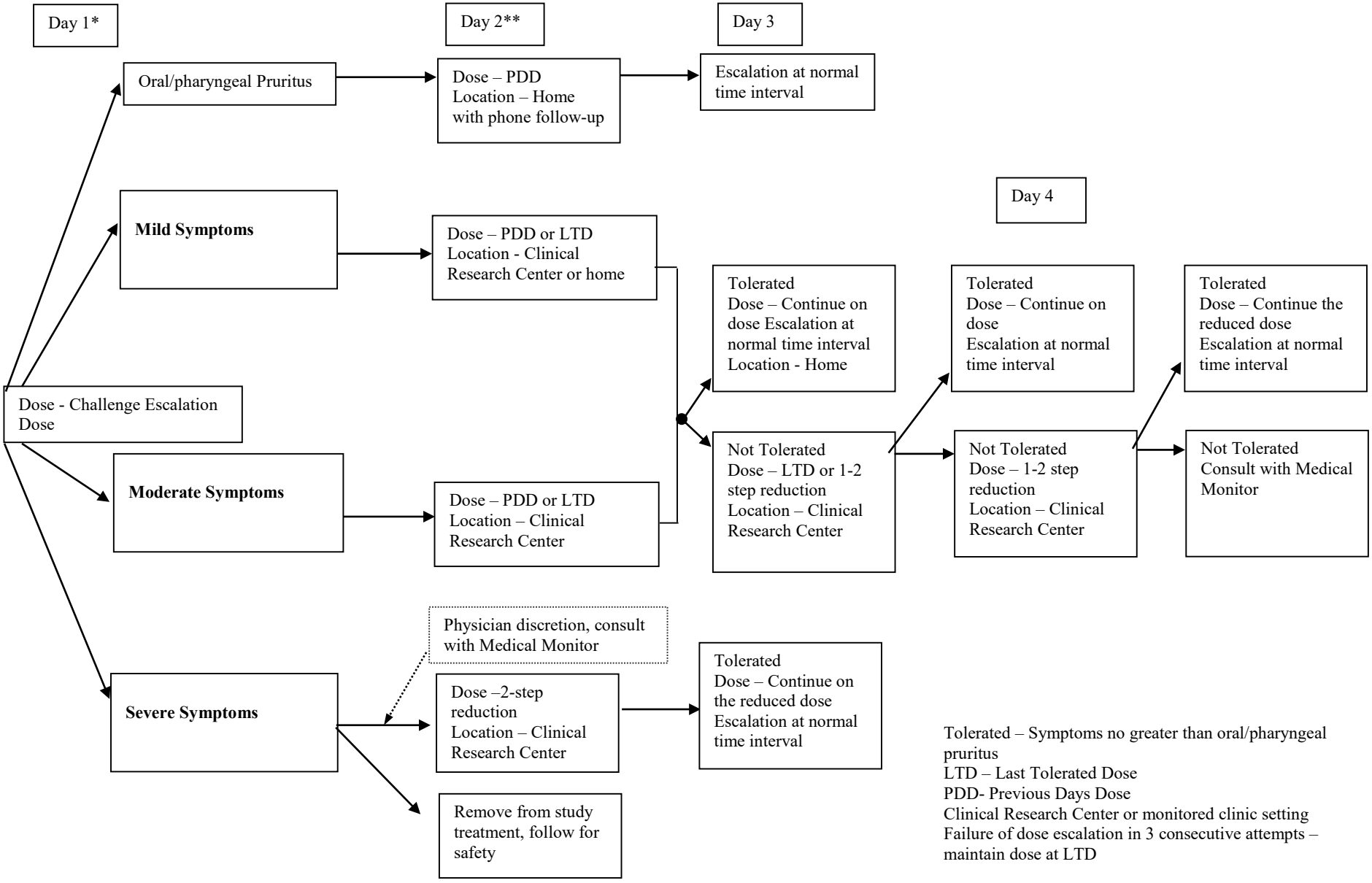


Figure 6–2. Schematic for Build Up Phase Dose Escalation – Day of Symptom



6.9 Missed Peanut OIT Doses at any Phase of the Study:

Missed Peanut OIT doses at any phase of the study can pose a significant risk to the enrolled subjects. The algorithm for missed consecutive doses of study product is as follows:

- Miss 1 dose – The next dose would be the current dose and could be given at home
- Miss 2 doses in a row – The next dose would be the current dose and could be given at home
- Miss 3 doses in a row – The next dose would be the current dose and would be given under observation (Clinical Research Center)
- Miss 4 doses in a row – The next dose would be the current dose and would be given under observation (Clinical Research Center)
- Miss 5-7 doses in a row –Initiate the next dose as approximately 25% of the last tolerated dose. This would be done under observation (Clinical Research Center). Dose escalation would occur in the Clinical Research Center with an escalation no sooner than weekly and no longer than every 4 weeks with dose increases of 1-dose levels at each escalation. If symptoms occur, the dosing symptom rules in the build-up phase would apply
- Missing >7 consecutive days of therapy constitutes an individual stopping rule and the subject would no longer take the study product. The subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**)
- Additionally; excessive missed doses, i.e., > 3 consecutive days missed on 3 occasions, constitutes an individual stopping rule and the subject would no longer take the study product. The subject will be asked to return to the Clinical Research Center 14 days following their last dose of study product to undergo an Early Discontinuation Visit (see **Section 6.5**).

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

6.10 Double-Blind Placebo Controlled Food Challenge

The subject will be off antihistamines for an appropriate length of time (5 half-lives of the antihistamine that is being used). Oral food challenges will be undertaken under direct medical supervision in a Clinical Research Center or food challenge area with emergency medications and staff immediately available and will follow established study procedures. Prior to the DBPCFC, subjects will be assessed for an exacerbation of asthma as determined by active wheezing or a peak expiratory flow rate < 80% of predicted. A uniform approach for food challenges will be used. Frequent assessments will be made for symptoms affecting the skin, gastrointestinal tract, cardiovascular system, and/or respiratory tract. Dose limiting symptoms, typically objective symptoms (signs), indicate a positive reaction and termination of dosing.

6.11 Skin Prick Test

Subjects will have skin prick tests performed using study approved procedures for food allergens. While the subject is off antihistamines for an appropriate length of time (5 half-lives of the antihistamine that is being used), a skin test probe is pressed through a commercial extract of an allergen into the epidermis. Positive (histamine) and negative (saline-glycerin) controls are placed to establish that the response is not blocked and to determine if there is dermatographism, respectively.

6.12 Visit Windows

Dosing schedule should be adhered to strictly. Two days before, or 2 days after a planned dosing visit, is an acceptable window with continued daily dosing of the current dose level. Study visits for scheduled blood draws or DBPCFC should take place within 2 weeks of the scheduled visit.

6.13 Study Blinding Procedures

The study is double-blinded up to completion of the exit DBPCFC, escalation failure, or endpoint failure.

Those who are not eligible for the DBPCFC at Week 34 will be unblinded at this time.

Those who do not pass the DBPCFC at Week 36 will be unblinded at this time.

All food challenges are performed in a double-blind manner.

6.13.1 Securing Blinding and Randomization Information

ARC or contractor will manufacture, package, label, store, and distribute the study product. During site visits, the site monitor checks the pharmacist or clinic logs to ensure that appropriate randomization assignments are received, recorded, and maintained.

6.13.2 Requirements for an Unblinding

Prior to the exit DBPCFC assessment, a subject can be unblinded only when needed for making medical decisions regarding the care of a subject. The decision of unblinding will be made in collaboration with the sponsor's Medical Monitor.
If a life-threatening event occurs, the subject should be treated as if the subject received active study product. For all unscheduled events that require unblinding, the investigator will contact the clinical monitor who will coordinate with the sponsor's representatives.

6.13.3 Breaking the Blind

In case emergency unblinding is necessary, TEMPO™ allows study personnel with appropriate permissions to request unblinding for a specific subject. An email is then sent to appropriate sponsor and CPWW safety designees informing them of the blinding. A built-in audit trail documents the unblinding process and the persons involved.

6.13.4 Documenting an Unblinding

Any premature unblinding requires a full written account by the site study physician of the event(s) that necessitated unblinding of the study medication for an individual participant. This account includes the reason(s) for unblinding, the name of the sponsor's medical monitor who was notified of the unblinding, the names of the unblinded individual staff members and the date and time the unblinding occurred.

7. Safety Monitoring

This section defines the types of adverse events that should be reported and outlines the procedures for appropriately collecting, grading, recording and reporting them.

7.1 Definitions for Recording of Safety Events

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

- Safety events related to accidental food exposure are recorded on a Food Allergy Episode form and are not reported on an adverse event form unless the event is considered a serious adverse event, as defined below (**Section 7.2**).
- Any allergic symptoms due to dosing will be recorded directly on the Escalation Dosing form (also referred to as a Study Product Administration form).
- For any event occurring after a subject has signed the informed consent form that meets the definition of anaphylaxis, an Anaphylaxis Episode form will be completed and forwarded to the Coordinating Center within 24 h of its occurrence and/or the sites being notified of the event (see also **Section 7.7.2**), if the event is associated with any of the following:
    - An emergency room visit;
    - Hospitalization;
    - More than 2 doses of epinephrine being given as treatment for the same episode;
    - Assessment of the anaphylaxis as severe, as defined in **Appendix 3**.
- If any safety event meets the definition of a serious adverse event (whether or not related to dosing), it will also be recorded on an adverse event (AE)/serious adverse event (SAE) form. Skin prick test and food challenge reactions that occur in the clinic are captured on study specific forms and are not reported on an adverse event form unless the event is considered a serious adverse event, as defined below. All serious adverse events are reported on the AE/SAE form set in addition to the Skin Prick form or an Oral Food Challenge form if the event occurred during one of these procedures. All other safety events that occur throughout the study are reported on the AE/SAE form set.

7.2 Food Allergy Episodes

In order to report the occurrence of a safety event associated with accidental food ingestion, subjects will be instructed to contact the site study coordinator or investigator

for any adverse event. The subject may be asked to return to the site. These events will be reported as follows:

- A Food Allergy Episode form will be completed for each of these events in addition to events where consumption of peanut without a reaction occurs.
- If the accidental food ingestion safety event meets the definition of a serious adverse event, as defined below, the AE/SAE form will be completed as well.

7.3 Definitions

7.3.1 Adverse Event (AE) or Medical Event

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

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

Adverse reaction is any adverse event caused by the drug.

7.3.2 Serious Events (Serious Adverse Events, Serious Suspected Adverse Reactions or Serious Adverse Reactions)

A serious adverse event including a serious suspected adverse reaction or serious adverse reaction as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

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

7.3.3 Unexpected Adverse Event

An adverse event is “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, the investigator’s brochure or the protocol.

7.4 Data Monitoring Committee

Although the safety of peanut OIT overall is well established, a Data Monitoring Committee (DMC) has been established to monitor the study for safety. The DMC Charter is under development and a plan has been drafted.

7.5 Toxicity Grading

The study site assigns toxicity grades to indicate the severity of adverse experiences and toxicities. The CoFAR adopted usage of NCI-CTCAE v 4.0 for application in adverse event reporting and will likewise be used for this protocol. The allergic reactions in this protocol are defined beyond the NCI-CTCAE system, and include further characterization of anaphylaxis. Anaphylaxis is characterized as mild, moderate, or severe in **Appendix 3**, independent of the toxicity grade associated with the event. Toxicity grading for allergic reactions including anaphylaxis is modified from the NCI-CTCAE system to be more appropriate for this study population, and is displayed in **Table A4-2** in **Appendix 4**.

The NCI-CTCAE v 4.0 was specifically reviewed for this protocol and is appropriate for this study population. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatment-related toxicities.

The NCI-CTCAE provides a term and a grade that closely describes the adverse event. Each participating site will receive copies of the grading scales and event descriptions.

Record adverse events not included in the NCI-CTCAE listing and grade them 1 to 5 according to the General Grade Definition provided below:

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

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

7.5.1 Guidelines for Determining Causality of an Adverse Event

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

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

7.6 Adverse Events Collection Procedures

Any new event or experience that was not present at Screening, or worsening of an event present at Screening, is considered to be an AE. Unchanged, chronic conditions are not AE's and should not be recorded on the AE page of the CRF. Adverse events will be evaluated from the onset of the event until the time the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.

AEs may be discovered through any of these methods:

- Observing the subject
- Questioning the subject, which should be done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records/source documents
- Review of home dosing symptom logs (provided to record symptoms between visits

7.6.1 Recording and Reporting Procedures

A multi-page adverse event form will be used allowing all adverse events to be submitted through a single reporting mechanism. Serious adverse events will require additional information reported on additional pages within the Internet data entry system. Source documents, with subject identifiers redacted, can be scanned and attached to the adverse event form as well. The investigator will treat subjects experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

7.6.2 SAE Recording and Reporting Procedures

Serious adverse events will be recorded on the adverse event case report form (CRF). All centers are obligated to report SAEs within 24 h of their occurrence and/or the site's knowledge of the event to the Coordinating Center. The following attributes will be assigned:

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

- Action taken

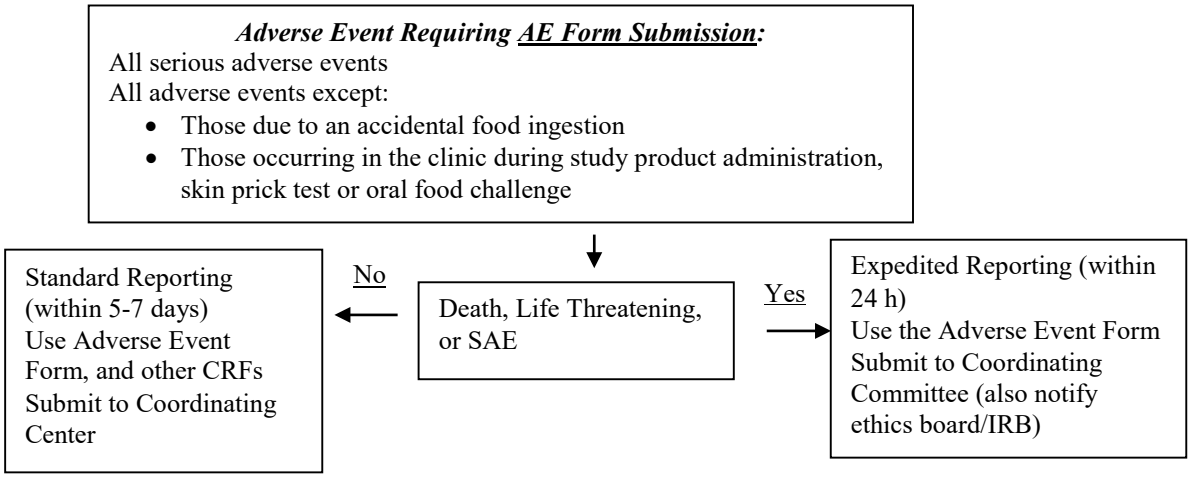
The site investigator will apply his/her clinical judgment to determine whether an adverse event is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator will suspend any trial procedures and institute the necessary medical therapy to protect a subject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

Subsequent review by FDA, the DMC, Institutional Review Board (IRB), or the sponsor(s) may suspend further trial treatment or procedures at a site. The study sponsor(s) and the FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

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

7.6.2.1 Reporting Criteria

Figure 7–1. Reporting Decisions for Adverse Events



1. Notify the site's investigator.
2. Complete and transmit an AE Form through the Internet data entry system. Information regarding a SAE report must be recorded in the subject's medical chart.
3. SAE follow-up reports should include hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment and any other pertinent information regarding the event. Reporting should not be delayed in order to provide these documents.
4. In the event of a death, the SAE Form must be completed and transmitted along with other supporting data (e.g., death certificate, medical notes, etc.).

7.7 Serious Adverse Event Notification

7.7.1 Notifying the Sponsor

Study investigators will provide the Coordinating Center with data of all SAEs as defined per the protocol on an ongoing basis.

The CRO Medical Monitor is responsible for notifying the sponsor and will do so simultaneously with the reporting to the clinical database. As noted above, this should be within 24 h of site awareness of the event. The sponsor's Medical Monitor will review each SAE report and will determine whether the SAE must be reported to FDA on an expedited basis. The final decision for disposition regarding reporting to the FDA rests with the sponsor's Medical Monitor. The IND Sponsor is responsible for submitting the SAE reports to FDA. The IND Sponsor will provide the DMC and the Coordinating Center with copies of any SAE reports submitted to FDA by the sponsor.

The Coordinating Center will provide these expedited reports to the individual site investigators. Events that are serious, related to therapy and unexpected will be reported to FDA in 15 days or for deaths and life threatening events in 7 days (per 21 CFR 312.32).

7.7.2 Notifying the Data Monitoring Committee

The Coordinating Center will provide the DMC with listings of all SAEs on an ongoing basis. Furthermore, the DMC will be informed of expedited reports of SAEs. Reports from DMC ongoing protocol safety reviews will be sent to the investigators.

Per DMC request, centers are instructed to report episodes of anaphylaxis within 24 h of their occurrence and/or the sites being notified of the event to the Coordinating Center if the event is associated with any of the following:

- An emergency room visit;
- Hospitalization;
- More than 2 doses of epinephrine being given as treatment for the same episode;
- Assessment of the anaphylaxis as severe, as defined in **Appendix 3**.

An initial Anaphylaxis Episode form containing the information known to the site at this time will be transmitted to the Coordinating Center. The Coordinating Center will then relay to the sponsor and DMC the individual anaphylaxis reports as they are obtained. The investigational site will supplement the initial Anaphylaxis Episode report with additional information pertaining to an event as it becomes available and will forward the information to the Coordinating Center.

7.7.3 Notifying the Institutional Review Board and Ethics Committee

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

7.8 Other Safety Assessments

7.8.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in **Appendix 1** Schedule of Events. Height and weight will also be recorded. Vital signs will also be assessed, including blood pressure (BP), pulse rate (PR), and body temperature.

7.8.2 Prior and Concomitant Medications

Prior and concomitant medications will be duly documented in the CRF.

7.8.3 Pregnancy Test

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

7.9 Stopping Rules

7.9.1 Overall Stopping Rules

The study will be suspended at any time such that a treatment-associated death occurs, or that the second of two subjects is admitted to the hospital as a direct consequence of dosing with study medication. The DMC will also be continually reviewing unblinded safety data, and can also recommend, in its judgment, halting the study for any substantial imbalance in adverse events, apart from dosing symptoms. The study will not be resumed until this information has been discussed with FDA and the FDA concurs with resumption of the study.

Allergen Research Corporation additionally reserves the right to discontinue the study at any time for any reason.

7.9.2 Individual Stopping Rules

Individuals may stop the study at any time if they experience subjectively intolerable adverse events or dosing symptoms. They must halt up-dosing and re-start with a reduced dose if more than three days of dosing are missed. Seven or more days of missed dosing constitutes an individual stopping rule, as does a significant number of episodes of missed dosing (ie, three or more days on at least three occasions). For additional individual stopping rules, the reader is referred back to **Section 4.3.1**.

Failure to accomplish up-dosing after three attempts will result in halting further up-dosing attempts, with the subject maintained at the previously achieved level. In addition, administration of two or more doses of epinephrine for the treatment of dose-related allergic reactions will result in halting further up-dosing attempts, with the subject maintained at the previously achieved level.

8. Mechanistic Assays

Complementary studies will be performed to measure humoral immune responses at baseline and at 6 months.

- Measurement of antigen-specific IgE and IgG4 levels
- SPT to peanut

8.1 Peanut-Specific Antibody

Antigen immunotherapy has been shown to induce antigen-specific humoral responses. The balance of isotypic response may play a role in allergen sensitivity (e.g., an increase of IgG/ IgE).

At each of the mechanistic time points, a sample of plasma will be stored for assessment of peanut specific antibody levels. Total IgE and specific IgE and IgG4 will be measured using UniCAP. Peanut specific IgE and IgG4 blood draws will be measured at screening and at Visit 03, with the amount of blood to be drawn determined by individual laboratory protocol.

9. Statistical Considerations

This protocol is a randomized evaluation of peanut OIT versus placebo therapy and baseline for individuals with peanut allergy.

9.1 Study Endpoint Assessment

9.1.1 Primary Endpoint

The primary endpoint is the proportion of subjects who achieve desensitization as determined by tolerating at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC (ie, responders).

Those who fail to achieve the target maintenance dose of at least 300 mg of study product will be considered as non-responders. An intent-to-treat analysis will be performed to test for a treatment difference in the response rate. All individuals failing to achieve the success definition described above will be considered failures. All individuals who drop out of the study or discontinue OIT will be considered failures, unless they have added *ad libitum* peanut consumption to their diet otherwise. Analysis will be via Chi-square test at the 0.05 significance level.

9.1.2 Secondary Endpoints

The secondary endpoints are defined in **Section 3.7**.

9.2 Subject and Demographic Data

9.2.1 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all enrolled subjects. Demographic data will include age, race, sex, body weight and height; these data will be presented in the following manner:

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

Statistical presentation for baseline and demographic characteristics may be further summarized by treatment group and baseline peanut-specific serum IgE.

9.2.2 Use of Medications

All medications used will be coded using the World Health Organization (WHO) drug dictionary. The number and percentage of subjects receiving concomitant medications or therapies will be presented. Statistical presentation of concomitant medications or therapies may be further summarized by treatment group.

9.2.3 Study Completion

The percent of subjects who complete the study, losses to follow-up, times to lost to follow-up and reasons for discontinuation (e.g., adverse events) will be presented. Statistical presentation of study completion will be further presented via analysis of the secondary endpoints summarized.

9.3 Sample Size and Power Calculations

While natural history of peanut allergy desensitization is not fully understood, significant short-term improvements in consumption amounts are believed to be uncommon. A true placebo response rate of 25% or less among subjects who undergo the exit DBPCFC is assumed in this study. Those individuals who fail to achieve the target daily dose or who withdraw prematurely will be treated as non-responders. We will recruit approximately 50 subjects.

If 3 subjects in each arm (about 12%) do not undergo the exit DBPCFC, then the effective placebo response rate in the ITT analysis is assumed to be 22% or less. With a 2-tailed 5% level test, there is at least 80% power to detect an effective CPNA response rate of 58.7% or more, which corresponds to a CPNA response rate of 66.7% or more among those who undergo the exit DBPCFC.

If 5 subjects in each arm (about 20%) do not undergo the DBPCFC, then the effective placebo response rate in the ITT analysis is assumed to be 20% or less. With a 2-tailed 5% level test, there is at least 80% power to detect an effective CPNA response rate of 56.6% or more, which corresponds to a CPNA response rate of 70.75% or more among those who undergo the exit DBPCFC.

10. Identification and Access to Source Data

10.1 Web-Based Data Collection and Management System

Data collection will occur via a web-based data entry system to allow easy access to enrollment 24 h a day, 7 days a week. Upon enrollment, a form submission schedule is generated for each subject and displayed as a grid of forms by study visit that permits direct access to each electronic CRF for data entry. As data are entered, they are validated through range and within-form consistency checks. The investigator must ensure that all web-based CRFs are completed in a timely fashion for each subject in the study.

10.2 Certification in the Use of Web-Based Data Entry System

The clinic and laboratory staff will be trained in the use of the data entry and specimen-tracking systems. Once certified, users are permitted to enter data into the production system. Access is password controlled. Certification for use of the web-based data entry system will be completed via telephone and/or web-cast training.

10.3 Data Management

Information regarding the subject's history, laboratory tests, nutritional intake, evaluation of allergic response and follow-up status will be stored and processed through the data center. Quality control procedures and a feedback system between the data center and the sites will be instituted to ensure the accuracy and completeness of the data collected.

10.4 Access to Data

The investigational sites shall periodically permit authorized representatives of the IND sponsor, and/or regulatory health authorities to examine clinical records and other source documents for the purpose of safety monitoring, quality assurance reviews, audits and evaluation of the study progress throughout the entire study period. The investigator is required by law (21 CFR 312.62) to keep accurate case records for at least 2 years after acceptance of a licensure application and FDA is notified, and record observations to assure the safe conduct of the study.

11. Quality Control and Quality Assurance

11.1 Statement of Compliance

This study will be conducted using good clinical practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance", and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB as well as FDA. Any amendments to the protocol or must also be approved by the sponsor, DMC, IRB and submitted to the

FDA before they are implemented. Any amendments to the consent materials must also be approved by the sponsor and IRB before they are implemented.

11.2 Informed Consent/Assent

The informed consent form is a means of providing information about the study to a prospective subject's parent/guardian and allows for an informed decision about participation in the study. Because the study population will be comprised of a significant percentage of children, parents or legal guardians will be asked to read, sign and date a consent form before a child enters the study, takes study product, or undergoes any study-specific procedures. Children will sign an assent as appropriate. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The informed consent form will be revised whenever the protocol is amended. A copy of the informed consent will be given to a prospective parent/guardian for review. The attending physician, in the presence of a witness, will review the consent and answer questions, as well as emphasize the need to avoid allergen exposure other than to Characterized Peanut Allergen, and the necessity to continue exposure to Characterized Peanut Allergen to maintain de-sensitization. The prospective parent/guardian will be told that being in the study is voluntary and that he or she may withdraw his/her child from the study at any time, for any reason.

11.3 Privacy and Confidentiality

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

12. Resource Sharing

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

13. Protocol Deviations

The investigators and site staff will conduct the study in accordance to the protocol. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Whenever applicable, corrective actions will be developed by the site and implemented promptly as a result of protocol deviations.

13.1 Major Protocol Deviation (Protocol Violation)

A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of

human subject protection regulations, or policies, any action that is inconsistent with medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

13.2 Non-Major Protocol Deviation

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

13.3 Reporting and Managing Protocol Deviations

Non-Major Protocol Deviations related to data entry or visit adherence are captured within the data system and are not additionally reported on a separate CRF.

The study site Principal Investigator has the responsibility to identify, document and report protocol violations/deviations and appropriate corrective action plans which are described above. However, protocol violations/deviations may also be identified during site monitoring visits or during other forms of study conduct review. All protocol violations will be reported in the data system on a specific CRF.

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Appendix 1: Schedule of Events

	Screening	Blinded Treatment				Exit/Early Discontinuation
Procedure	**Visit 00 Screening**	**Baseline Visit**	**Visit 01 Initial Escalation (Day 1-3)[1]**	**Up-dosing visits (approx. every 2 wks for 24 wks)[2]**	**Visit 02 (approx. 12 wks)**	**Visit 03**
Informed consent	X	X				
Inclusion/exclusion criteria	X	X				
Medical/allergy history	X	X			X	X
Concomitant medications	X	X	X	X	X	X
Physical exam, including weight and height	X	X	X	X	X	X
Vital signs (BP, PR, temperature)	X	X	X	X	X	X
Peak flow rate (PEFR)[3]	X	X	X	X	X	X
Pregnancy test[4]	X serum	X urine			X urine	X urine
Diet history	X		X		X	X
Blood draw for peanut specific IgE, IgG4	Pre-DBPCFC					Pre-DBPCFC
Optional blood draw for ITN exploratory analysis[5]	Pre-DBPCFC					Pre-DBPCFC
	5-10 days post-DBPCFC					
Skin prick test	X					X
Clinical Research Center study product administration			X	X	X	X
Dispensing study products for home dosing/Return of unused products			X	X	X	
Physician Global Assessment		X				X
Dose assessment to decide for maintenance or up-dosing						X

	Screening	Blinded Treatment				Exit/Early Discontinuation
Procedure	**Visit 00 Screening**	**Baseline Visit**	**Visit 01 Initial Escalation (Day 1-3)[1]**	**Up-dosing visits (approx. every 2 wks for 24 wks)[2]**	**Visit 02 (approx. 12 wks)**	**Visit 03**
Double-blind, placebo controlled food challenge (DBPCFC) PRACTALL guidelines	X					X[6]
Telephone monitoring of dosing compliance and symptoms[7]			X 1 wk after visit	X	X	X
Adverse events[8]			X	X	X	X

1. Visit 01: Escalation to at least 3.0 mg on Day 1, return Day 2, return Day 3 if symptoms present, return for dose escalation every 2 weeks. Dose escalation schedule is shown in **Table 3-1**.
2. Up-dosing visits: every 2 .weeks at clinic, unless epinephrine is administered as described in Section 6.8. Dose escalation schedule is shown in **Table 3-1**
3. Prior to any DBPCFC and at Baseline; 3 attempts, best value taken; should be measured at the same time for each visit assessment
4. For females of childbearing potential
5. For subjects ≥30kg only, at 5 mL/kg, with a maximum of 60 mL in total; analysis by ITN.
6. Eligible subjects (up-dose to 300 mg plus 2 weeks on 300 mg) only will undergo a DBPCFC at the exit visit.
7. Phone calls will occur 1 week after each escalation visit to assess dosing compliance and symptoms. Schematic for symptoms is described in **Figure 6–1** and **Figure 6–2**.
8. AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.

Appendix 2: Evaluation of Asthma

The evaluation of asthma severity will be assessed using the NHLBI classification published August 28, 2007 as described in the table below.

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

*Normal FEV1/FVC: 8-19 yr = 85%; 20-39 yrs = 80

Appendix 3: Anaphylaxis Staging System

Staging System of Severity of Anaphylaxis[27]	
Stage	**Defined By**
1. *Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)*	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)	Marked dysphagia, hoarseness and/or stridor; shortness of breath , wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Criteria for Diagnosis[28]

Anaphylaxis is likely when any one of the three following sets of criteria is fulfilled:

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

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

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

Appendix 4: Allergic Reaction Toxicity Grading

Current NCI-CTCAE v. 4.03 grading system for allergic reactions defined as a disorder characterized by an adverse local or general response from exposure to an allergen.

Table A4-1: Current NCI-CTCAE v. 4.03 Grading System for Allergic Reactions

Grade 1 - Mild	Grade 2 - Moderate	Grade 3 – Severe	Grade 4 – Life-Threatening	Grade 5 – Death
Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death

Current NCI-CTCAE v. 4.03 grading system for anaphylaxis reactions defined as a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

Table A4-2: Current NCI-CTCAE v. 4.03 Grading System for Anaphylaxis Reactions

Grade 1 - Mild	Grade 2 - Moderate	Grade 3 - Severe	Grade 4 – Life-Threatening	Grade 5- Death
-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

These tables will be replaced with the CoFAR specific grading system for allergic reactions as displayed in **Table A4-3**.

Table A4-3: CoFAR Specific Grading System for Allergic Reactions

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