STATISTICAL ANALYSIS PLAN

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

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Aimmune Therapeutics, Inc.
8000 Marina Blvd, Suite 300
Brisbane, CA 94005
United States

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PREPARED BY:	Clinipace Worldwide
AUTHORS:	**Venita DePuy, PhD**

APPROVAL SIGNATURES

SIGNATURE: DATE:

15 Dec '14

Robert Elfont, MD, PhD
Chief Medical Officer
Allergen Research Corp.

Ron Marks

15 DEC 2014

Ron Marks, PhD
Chief Scientific Officer
Clinipace Worldwide

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Class
DBPCFC	Double-blind placebo-controlled food challenge
DMC	Data Monitoring Committee
CI	Confidence Interval
CPNA	Characterized Peanut Allergen
eCRF	electronic Case Report Form
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
ITN	Immune Tolerance Network
ITT	Intent-to-Treat
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MTD	Maximum Tolerated Dose
OIT	Oral Immunotherapy
PEFR	Peak Expiratory Flow Rate
PRACTALL	PRACtical Issues in ALLergology, Joint United States/European Union Initiative
PRN	As needed (*pro re nata*)
PT	Preferred Term
PP	Per Protocol
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment-Emergent Adverse Event
ULOQ	Upper limit of quantification
VAS	Visual Analog Scale
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of Protocol ARC001. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection. This document incorporates:

- Primary and key secondary efficacy analyses specified in the abbreviated Statistical Analysis Plan, version 1.0, dated 07 February 2014 (based on Protocol Amendment 2, dated 29Jan2014)
- Various clarifications to study design and study procedures and modification to the maximum dose at the Exit DBPCFC (based on Protocol Amendment 3, dated 14May2014)
- Clarification that consumption of 100 mg (not >100 mg) of peanut protein at the Screening DBPCFC constitutes grounds for screen failure.

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 Study Objectives

The purpose of this study is to determine the efficacy and safety of characterized peanut oral immunotherapy (OIT) in peanut-allergic children and young adults (ages 4 – 26 years, inclusive).

2.1.1 Primary Objectives

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

2.1.2 Secondary Objectives

The secondary objectives are:

- To demonstrate the safety of CPNA 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.

2.1.3 Exploratory Objectives

The exploratory objective is to evaluate the immunological effects of CPNA OIT on additional parameters.

2.2 Treatment Group Comparisons

Peanut OIT therapy will be compared to placebo for reduction in clinical reactivity to limited amounts of peanut allergen and safety of peanut OIT.

2.3 Study Endpoints

2.3.1 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 at the Exit double-blind placebo-controlled food challenge (DBPCFC) with no more than mild symptoms (i.e., desensitization responders).

2.3.2 Secondary Endpoints

2.3.2.1 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change from baseline (Screening DBPCFC) in tolerated dose of peanut protein at Exit DBPCFC
- Maximum dose achieved with no or mild symptoms at Exit DBPCFC
- Changes in peanut IgE and peanut-specific IgG4
- Changes in skin prick test (SPT) mean wheal diameters

2.3.2.2 Secondary Safety Endpoints

Secondary safety endpoints include:

- Safety of peanut OIT as measured through dosing symptoms, adverse events (AEs), and serious adverse events (SAEs).
- Physician global assessment: Disease activity as measured on a 100 mm visual analog scale (VAS)

2.3.3 Exploratory endpoints

Exploratory safety endpoints include:

- Epinephrine use
- Occurrence of anaphylactic reaction episodes

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study of efficacy, safety, and immunological effects of CPNA OIT in peanut-allergic

individuals. The study will consist of a screening period with a DBPCFC, a double-blind OIT treatment (up-dosing and maintenance) period, followed by an Exit DBPCFC. A total of approximately 50 peanut-allergic subjects will be randomized 1:1 to CPNA vs. placebo OIT, across approximately 8 study sites.

3.2 Schedule of Study Assessments

3.2.1 Screening Period

The screening visits (Visit 00) may occur over several days, and will include an initial DBPCFC. The DBPCFC will have both a peanut challenge and a placebo challenge, using up to 100 mg (143 mg cumulative) each of peanut protein and placebo, based on the PRACtical issues in ALLergology Joint United States/European Union Initiative (PRACTALL)[1] dosing regimen, as shown in Table 3.1. At the investigator's discretion, a 1 mg dose may be added at the beginning of the escalation.

Table 3.1. PRACTALL Screening DBPCFC Dosing Schedule

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

A DBPCFC is conducted either as two challenges during a single day visit (with at least 3 hours separating the two halves of the challenge) or over 2 days with the placebo challenge on one day and the peanut challenge on the other day. The food challenges are presented in random order and are performed under double-blind conditions.

Subjects who have dose-limiting symptoms at or before the 100 mg dose of peanut protein will be enrolled into the study. Those who successfully consume a dose of 100 mg of peanut protein during the Screening DBPCFC, without experiencing dose-limiting symptoms, will be considered 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 placebo [oat flour] as well as peanut flour) will be considered to be a screen failure and will not be randomized.

Subjects who meet eligibility criteria will return for a baseline visit, which may occur over multiple days. See Table 3.5 for the schedule of assessments.

3.2.2 Treatment Period (Visits 01, 02 and Up-dosing Visits)

The treatment up-dosing phase will start with an initial escalation (Visit 01) at the study center, followed by up-dosing for approximately 24 weeks, conducted in a double-blind fashion. Up-dosing will continue until the subject reaches a steady dose of 300 mg/day, is unable to continue escalation due to symptoms, or withdraws from the study. If a subject does not require any dose reductions during the up-dosing phase, the target maintenance dose of 300 mg/day will be reached in either approximately 18 or 20 weeks, depending on whether up-dosing was started at 6.0 or 3.0 mg/day, respectively. Once achieved, the target dose of 300 mg/day is to be maintained for 2 weeks, for a total of approximately 20 or 22 weeks of dosing after the initial escalation visit. If, however, a subject does require dose reductions during the up-dosing phase, the total duration of dosing after Visit 01 may be extended up to an additional 12 weeks, for a total duration of up to 34 weeks.

During Visit 01 (comprising 2 or 3 days), doses will be delivered at 20 to 30 minute intervals, as described in Table 3.2. 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 3.0 mg on Day 1 will return on Day 2 to receive their MTD (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. If the 3 mg dose is tolerated, subjects return home on that dose for 2 weeks until the next escalation. 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. 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	12.0

After the initial escalation visit, subjects will report to the study center every 2 weeks to escalate their OIT dose, up to a targeted daily dose of 300 mg/day of peanut protein as shown in Table 3.3. All escalation doses will occur in a Clinical Research Center or other monitored setting. Maintenance dosing between clinical visits will occur daily at home.

Subjects who achieve the targeted 300 mg/day by Week 34 will remain on 300 mg/day (maintenance phase) for at least 2 weeks, prior to undergoing the Exit DBPCFC (Visit 03). If, following Visit 01, dose escalation is halted for a subject (per Section 6.8.2 and 6.8.3 of protocol), that subject will continue to be dosed at their last tolerated dose until Week 24 (maintenance phase). 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.

Table 3.3. Escalation Dosing Schedule for Peanut OIT

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%

Visit 02 will occur after approximately 12 weeks post-Visit 01, and will include assessments as shown in Table 3.5. Up-dosing visits will occur both before and after Visit 02. Visit 02 may also be combined with a regularly scheduled up-dosing visit.

3.2.3 Exit Visit (Visit 03)

After approximately 24 weeks of randomized study treatment, eligible subjects who reach the targeted daily dose of 300 mg/day and maintain that dose for 2 weeks will undergo an Exit DBPCFC of up to 600 mg (1043 mg cumulative) peanut protein and placebo (see Section 6.6.2 of protocol). Subjects who have not reached 300 mg/day by Week 24 will continue to up-dose as tolerated until they are eligible for the Exit DBPCFC (after 2 weeks of at-home dosing with 300 mg/day). The Exit DBPCFC will be conducted in a manner similar to the Screening DBPCFC but with the dosing schedule as shown in Table 3.4. Note also that subjects are not scheduled for a dose of study product at home or in-clinic on the day of Visit 03.

Subjects who fail escalation, whose dose escalation is halted, and/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.

Table 3.4. PRACTALL 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

The schedule of study assessments will be as follows:

Table 3.5. Schedule of Assessments

	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

	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**
Dose assessment to decide for maintenance or up-dosing						X
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 of the protocol.
2. Up-dosing visits: every 2 .weeks at clinic, unless epinephrine is administered as described in Section 6.8 of the protocol. Dose escalation schedule is shown in Table 3-1 of the protocol.
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 of the protocol.
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.

4 SAMPLE SIZE CONSIDERATIONS

Sample size calculations are based on the primary efficacy analysis of the desensitization response rate. A true placebo response rate of 25% or less among subjects who undergo the Exit DBPCFC is assumed. Those individuals who fail to achieve the daily dose target or withdraw prematurely will be treated as non-responders. This study will enroll approximately 50 subjects randomly assigned in a 1:1 ratio of active to placebo.

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 (alpha=0.05) 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 Exit DBPCFC, then the effective placebo response rate in the ITT analysis is assumed to be 20% or less. With a 2-tailed (alpha=0.05) 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.

5 ANALYSIS POPULATIONS

5.1 Enrolled Population

The Enrolled population will consist of all subjects with completed informed consent.

5.2 Randomized Population

The Randomized population will consist of all randomized subjects. Subjects will be presented according to randomized treatment. The Randomized population will be used to present information on the overall study.

5.3 Safety Population

The Safety population will consist of all subjects who receive randomized study treatment. The Safety population will be used for summaries of safety parameters. Subjects will be analyzed according to treatment received. Any subject receiving at least 1 dose of CPNA during the study (not including food product administered during DBPCFC) will be categorized in the CPNA treatment group, regardless of randomization assignment.

5.4 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects who received at least one dose of randomized study treatment. Subjects will be analyzed according to randomized treatment. The ITT population will be used as the primary analysis population for all analyses of efficacy endpoints.

5.5 Modified Intent-to-Treat (mITT) Population

The mITT population will consist of all randomized subjects who received at least one dose of randomized study treatment and who have sufficient data to assess the primary efficacy endpoint. Subjects who withdraw early for reasons unrelated to treatment success or failure will be excluded. Withdrawals for escalation failure, treatment-related AEs and deaths, or the addition of *ad libitum* peanut consumption to diet will not be excluded. Exclusions will be determined by blinded review prior to database lock and unblinding. Subjects will be analyzed according to randomized treatment. The mITT population will be used for sensitivity and supportive analyses of the primary and key secondary efficacy endpoints.

5.6 Per Protocol (PP) Population

The PP population will be a subset of the mITT population, limited to subjects who have no major protocol deviations that may influence the desensitization response. With the exception of withdrawals for escalation failure and treatment-related AEs and deaths, all subjects who withdraw prematurely or have a major protocol deviation will be excluded from the PP population. Exclusions will be determined by blinded review prior to database lock and unblinding. Subjects will be analyzed according to randomized treatment. The PP population will be used for sensitivity and supportive analyses of the primary and key secondary efficacy endpoints.

5.7 Screening DBPCFC Only Population

The Screening DBPCFC Only population will consist of all subjects who underwent at least one part (peanut flour challenge or oat flour challenge) of the Screening DBPCFC, but did not receive any randomized study treatment.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

SAS® version 9.2 or higher will be used for statistical analyses and to produce tables, listings, and figures (if applicable).

6.2 Strata and Covariates

Demographic and baseline characteristics are evaluated by baseline peanut IgE level and baseline SPT wheal diameter, as described in Section 8.6. In addition, exploratory efficacy analyses will be used to evaluate the effect of baseline factors on peanut MTD at Exit DBPCFC and the change in peanut MTD, as described in Sections 9.5.1 and 9.5.2.

6.3 Subgroups

Demographic and baseline characteristics will be presented by baseline IgE level, as described in Section 8.6. There are no other planned subgroup analyses.

6.4 Multiple Comparisons and Multiplicity

The key secondary endpoints are tested in a hierarchical method, as described in Section 9.3. No other adjustments will be made for multiple comparisons.

6.5 Significance Level

Unless stated otherwise, all statistical tests will be two-sided, with a significance level of 0.05. Confidence intervals (CIs) will be calculated at the 95% level, reflecting a type I error rate of 0.05.

6.6 Statistical Notation and Methodology

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data and frequencies and percentages for categorical data. Unless noted otherwise, the denominator for percentages will use the number of subjects in the analysis population. Minimum and maximum values will be rounded to the precision of the original value, means, medians, first quartiles, and third quartiles will be rounded to 1 decimal place greater than the precision of the original value, standard deviations will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "<1%" and ">99%" shown as necessary for values falling near the boundaries.

7 DATA HANDLING METHODS

7.1 Visit Windows

All information will be listed, summarized, and analyzed according to the nominal visit. No visit windowing will be performed.

7.2 Data Presentation

Individual subject data listings will be provided to support summary tables and serve as a data source. Unless otherwise noted, all data collected during the study for subjects in the Randomized population will be included in data listings. No imputation, other than the imputation of desensitization response and MTD at Exit DBPCFC as described in Sections 7.3 and 7.4, will be included in listings. Listings will be sorted by treatment group, subject identifier, and visit date (where applicable). If a listing includes screen failures, they will be listed as treatment group 'NONE' and sorted after all randomized subjects.

Visit 02 and Updosing Week 12 will be combined for by-visit summaries. If a subject has a non-missing result recorded for both Visit 02 and Updosing Week 12 visits, the result from the assessment closest to the midpoint between the Updosing Week 10 and Updosing Week 14 visit will be summarized. If there is no Updosing Week 14 visit, the assessment closest to 14 days after the Updosing Week 10 visit will be used. If there is a tie, the Updosing Week 12 assessment will be used. This visit will be displayed as "Visit 02/ Updosing Week 12."

Unscheduled visits will be listed but not included in by-visit summaries. Results from unscheduled visits may be used as baseline values, and for other derivations not tied to visit names (for example, unscheduled visits are included in the determination of worst post-baseline values for physical examination results).

7.3 Maximum Tolerated Dose at DBPCFCs and Escalation Failures

The MTD for a DBPCFC is defined as the maximum single dose of peanut protein resulting in no more than mild symptoms and assessed by the investigator to have been tolerated (i.e., subject did not experience any dose-limiting symptoms). The MTD at the Screening DBPCFC will be used as the baseline amount of peanut protein tolerated. If a subject is administered non-standard doses at DBPCFC (i.e., other than the doses listed in Tables 3.1 or 3.4), the MTD will be considered the highest tolerated standard dose (i.e., 3 mg, 10 mg, 30 mg, 100 mg for either DBPCFC; 300 mg for Exit DBPCFC) which is tolerated.

An escalation failure is a subject who does not reach the target 300 mg/day dose by Week 34, or fails to complete at least a 2-week maintenance at that dose level.

Where necessary, desensitization response and MTD at the Exit DBPCFC will be imputed for subjects who do not have an Exit DBPCFC as shown in Table 7.1. As a general rule, subjects who do not undergo an Exit DBPCFC for any reason will be categorized as desensitization non-responders; and the imputed value for their MTD will be the maximum dose of peanut protein they tolerated in their Screening DBPCFC. The one exception to this rule is in the event of documentation that a subject introduced *ad libitum* peanut consumption into their diet and tolerated amounts of peanut exceeding a single peanut kernel (the targeted level of desensitization in the study). Although subjects are repeatedly and strenuously admonished, per protocol, to maintain a peanut-avoidant diet, there is always the potential for the admonishments to go unheeded, as well as for accidental exposure. In the unlikely event that a subject starts to consume peanut *ad libitum* before exiting the trial, whether or not this occurs as the result of a protocol violation, provision has been made for imputing their results (see Table 7.1). If, however, the amount of peanut consumed and tolerated by a subject claiming *ad libitum* peanut consumption cannot be ascertained from the eCRF or source documentation, then the subject will be classified as a non-responder who missed their Exit DBPCFC after having discontinued for reasons unrelated to treatment. If a subject added *ad libitum* peanut consumption to their diet and had additional reasons for missing the Exit DBPCFC, then the imputation rules for *ad libitum*

peanut consumption will be determined during blinded data review on a case-by-case basis.

Classification of responder and non-responder categories and subcategories, and reasons for missing the DBPCFC will be determined during blinded data review prior to database lock and unblinding, as described in Section 12.

Table 7.1 Imputation Rules for Desensitization Response and MTD

Response Subcategory for subjects missing Exit DBPCFC [1]	Reason for missing Exit DBPCFC	Imputation Rule for Desensi-tization Response	Imputation Rule for MTD at the Exit DBPCFC	Justification
Ad libitum peanut consumption	Added *ad libitum* peanut consumption to their diet	Responder, provided there is sufficient documentation for a peanut kernel or greater [4]	300 mg, provided there is sufficient documentation for a peanut kernel or greater [4]	Documentation available that the subject achieved at least the minimum targeted level of desensitization
Reached 300 mg/day target but DBPCFC not conducted	• Eligible for DBPCFC but it was not conducted due to at least one treatment-related reason, as entered on the eCRF [2] • Eligible for DBPCFC but it was not conducted only for reasons unrelated to treatment, as entered on the eCRF [2]	Non-responder	MTD at Screening DBPCFC	Unable to verify desensitization
Escalation failure	Fail to achieve the target maintenance study product dose of at least 300 mg/day and thus did not qualify for the Exit DBPCFC. Reasons include: • Discontinued as an escalation failure during initial escalation (Visit 01) [3] • Discontinued as an escalation failure during up-dosing prior to Week 24 [3] • Discontinued as an escalation failure after Week 24 [3] • Discontinued for treatment-related AE or death [3] • Discontinued for other reasons related to treatment [3] • Discontinued for reasons unrelated to treatment [3]	Non-responder	MTD at Screening DBPCFC]	Unable to verify desensitization

[1] Subjects will be assigned to only one response subcategory during blinded data review.
[2] More than one reason may be given for the DBPCFC not being conducted for a subject who reached the 300 mg/day target. Each reason will be classified as treatment-related, or not, during blinded data review.
[3] More than one reason for discontinuation may be given. Each discontinuation reason will be classified as treatment-related, or not, during blinded data review. Escalation failure is a specific reason for early discontinuation on the eCRF.
[4] Information from free text fields on the eCRF for protocol deviations or reason for early discontinuation will be used to determine the imputed value. If it is clear that an amount of peanut exceeding a single peanut kernel was regularly consumed without eliciting symptoms, then a value of 300 mg will be imputed. If the amount of peanut consumed cannot be ascertained or is less than the equivalent of a peanut kernel, then the subject will be classified as a Non-responder and no value will be imputed.

7.4 Classification of Responder Status

A desensitization responder is defined as a subject who achieves a desensitization response as determined by tolerating at least 300 mg (443 mg cumulative) of peanut protein (measured as 600 mg of peanut flour) at the Exit DBPCFC with no more than mild symptoms.

A non-responder is an escalation failure or a subject who experienced dose-limiting symptoms (moderate or worse) at or before the 300 mg dose of peanut protein during the Exit DBPCFC.

Additional classification of responder and non-responder categories are provided in Table 7.2.

Table 7.2 Response Categories

Response Category	**Response Subcategory [1]**	**Criteria**
Desensitization Responder	Passed Exit DBPCFC	Tolerate at least 300 mg (443 mg cumulative) of peanut protein at the Exit DBPCFC with no more than mild symptoms
	Ad libitum peanut consumption	Added *ad libitum* peanut consumption to their diet
Non-Responder	Failed Exit DBPCFC	Fail to tolerate at least 300 mg (443 mg cumulative) of peanut protein at the Exit DBPCFC with no more than mild symptoms
	Reached 300 mg/day but Exit DBPCFC was not conducted	Reasons [2] include: • Eligible for DBPCFC but it was not conducted due to at least one treatment-related reason, as entered on the eCRF • Eligible for DBPCFC but it was not conducted only for reasons unrelated to treatment, as entered on the eCRF
	Escalation Failure	Fail to achieve the target maintenance study product dose of at least 300 mg and thus did not qualify for the Exit DBPCFC. Reasons[3] include: • Discontinued as an escalation failure during initial escalation (Visit 01) • Discontinued as an escalation failure during up-dosing prior to Week 24 • Discontinued as an escalation failure after Week 24 • Discontinued for treatment-related AE or death • Discontinued for other reasons related to treatment • Discontinued for reasons unrelated to treatment

[1] Subjects will be assigned to only one response subcategory during blinded data review.
[2] More than one reason may be given for the DBPCFC not being conducted for a subject who reached the 300 mg/day target. Each reason will be classified as treatment-related, or not, during blinded data review.
[3] More than one reason for discontinuation may be given. Each discontinuation reason will be classified as treatment-related, or not, during blinded data review. Escalation failure is a specific reason for early discontinuation on the eCRF.

7.5 Data Derivations and Definitions

The following definitions and derivations will be used throughout this study:

- Study Day is calculated as (assessment date – first dose date + 1) for assessments and visits performed on or after the first dose date, and (assessment date – first dose date) for assessments and visits prior to the first dose date.
- Baseline is defined as the last non-missing value prior to the first dose of randomized study treatment.
- Change from baseline is calculated as observed value after the first dose – baseline value.
- The active treatment period is defined as the time period beginning with the date and time of the first dose of randomized study product, and ending with the date of the last dose of randomized study product taken prior to Exit DBPCFC.

7.6 Data Pooling

Data pooling will be performed as necessary for exploratory analyses, as described in Section 9.5. No other data pooling is planned.

7.7 Maintenance of the Study Blind Prior to Database Lock

Due to the nature of the study, some data will be suggestive of randomized treatment assignment (specifically: allergy symptoms during dosing; Exit DBPCFC results; and adverse events, anaphylaxis episodes, concomitant medications and therapies, and IgG4 & IgE lab results after the first dose of randomized study treatment). The following procedures will be implemented to assist in maintaining the study blind among project team members during blinded data reviews prior to database lock (see also Section12):

- All tables and figures will be produced using surrogate randomization.
- All listings will have subject numbers masked by a randomly created subject identifier, which will be the same for each subject across listings. Listings may also include the surrogate randomized treatment used in the tables.

Although the study statistician and programming team does not have access to treatment assignments, they do have access to the actual subject identifiers and safety and efficacy data potentially suggestive of treatment assignment on a subject level basis. As a precaution, all advice by the lead statistician regarding study conduct issues will be documented. If a conflict arises, the lead study statistician will inform the project team, and if appropriate, the sponsor statistician and/or another statistician will be designated for this task. The study statistician

may attend decision-making meetings (see Section 12) to provide information as requested, but will not be involved in the decisions.

The sponsor statistician will not have access to the ARC002 treatment assignments (directly based on ARC001 treatment assignments) for subjects who roll over into ARC002. Similarly, the sponsor statistician will not have access to listings with actual subject identifiers or treatment information, and will not have access to the TEMPO database to view data directly. The sponsor statistician will receive subject listings, with surrogate and masked information as described above. The sponsor statistician will remain thusly blinded, in order to contribute to unbiased decisions made by the sponsor (see Section 12).

Other sponsor representatives have access to subject tracking information, e.g., the dates of up-dosing visits, and will have access to ARC002 treatment assignments upon subject enrollment in that study, that, if combined, could be suggestive of treatment assignment on a subject level basis. These sponsor representatives may, however, still review blinded tables, with surrogate treatment information. Sponsor representatives involved in the pre-database lock blinded data review will only have access to a limited number of masked listings for conducting that blinded review (see Section 12). Additionally, the sponsor medical monitor and other sponsor representatives will have access to the masked listings described below in Table 7.3 for the purpose of ongoing safety review during the conduct of the study.

Table 7.3 Masked Listings for Ongoing Safety Monitoring

Output ID / Title	Frequency
LO1 Adverse Events	Monthly
LO2 Concomitant Medications: Epinephrine Rescue Medications	Monthly

7.8 Randomization, Treatment Assignments, and Blinding

Subjects are randomized in a 1:1 ratio to each study treatment (CPNA or placebo) using the TEMPO system. A central randomization schedule of randomly permuted blocks was prepared by an independent unblinded statistician for use in the TEMPO system.

Subjects will be unblinded after the final visit is completed and they exit the ARC001 trial. Subjects who withdraw and do not complete their final visit assessments will be unblinded after they exit from the study. End of study (scheduled) unblinding will be requested by the site. Emergency (unscheduled) unblinding for safety reasons may also occur, as described in the protocol. Emergency unblinding may be requested by the site or other study team members (such as the medical monitor).

For either type of unblinding, the date of unblinding, type (scheduled or unscheduled), and person who requested the unblinding will be processed and documented in TEMPO. The actual treatment assignment will be made available only to the person requesting unblinding. Other study team personnel will receive

notification that the treatment assignment has been provided, but will not be notified of the actual treatment assignment.

Masking procedures for outputs provided only to the Data Monitoring Committee (DMC) are described in the DMC Charter.

7.9 Database Lock and Unblinding

Once the database has been locked, randomized treatment assignments will be obtained from the TEMPO system following standard procedures. These treatment assignments will then be incorporated into the analysis datasets, tables, listings, and figures.

8 STUDY POPULATION

Unless otherwise noted, the Randomized population will be used for listings and summaries of overall study.

8.1 Analysis Populations

The analysis population listing will include, for each population detailed in Section 5, whether or not the subject was included in the population and the reason for being excluded from the population. Number of subjects in each analysis population will be summarized overall and by treatment group.

8.2 Subject Enrollment and Randomization

The dates and times of informed consent, whether informed assent by the minor subject is required, and date and time of informed assent, will be listed for all enrolled subjects.

Subject eligibility for randomization, whether subject proceeded to randomization, randomized treatment group, and reason subject not randomized (if applicable), will similarly be listed for all enrolled subjects.

8.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria responses will be summarized in a data listing that displays whether all eligibility criteria were met, and what inclusion/exclusion criteria were not met. This listing will be presented for all enrolled subjects.

8.4 Subject Disposition

Subject disposition will be recorded in the eCRF, either at the final follow-up visit or when a subject discontinues the study or is lost to follow-up. The number of subjects who enroll, complete the study, discontinue from the study, and reasons for study discontinuation will be summarized.

Number of days on study is calculated as (date of discontinuation – first dose date + 1) for subjects who discontinue the study, and (last study visit date – first dose date + 1) for subjects who complete the study. The number of days on study will be summarized for subjects who were lost to follow up.

8.5 Protocol Deviations/Violations

Major and minor protocol deviations will be recorded in the TEMPO system. The following categories of deviations will be recorded:

- Subject did not satisfy the entry criteria
- Subject developed withdrawal criteria during the trial and was not withdrawn
- Subject dispensed wrong treatment
- Subject dispensed incorrect dose
- Subject received prohibited medication
- Subject non-compliance
- *Ad libitum* peanut consumption
- Other (with free text field to record details).

These protocol deviations will be reviewed in blinded fashion prior to database lock, as described in Section 12, and their categorization as major or minor will be determined prior to database lock.

All protocol deviations will be listed by subject. Major protocol deviations will be summarized by treatment group and overall.

8.6 Demographic and Other Baseline Characteristics

Demographic information, in addition to the MTDs of peanut and placebo at the Screening DBPCFC, and the presence of dose limiting symptoms and associated dose levels at the Screening DBPCFC, will be listed for all enrolled subjects. The baseline physicians' global assessment of disease activity will also be listed.

Age in years, at Screening, will be calculated using the following SAS formula:

```
AGE=floor(yrdif( birthdate ,  Informed Consent date , 'AGE'));
```

Demographic characteristics, including sex, race, ethnicity, age, height, weight and BMI, will be summarized by treatment group and overall. Baseline immunological characteristics (including total IgE, peanut IgE, peanut-specific IgG4, peanut-specific IgE/IgG4 ratio, and results from SPT) as well as maximum tolerated dose of peanut protein at Screening DBPCFC, and baseline global assessment of disease activity per the VAS, will also be summarized by treatment group and overall.

Demographic and baseline characteristics will be summarized by baseline peanut specific IgE level (less than or equal to 15 kU/L versus greater than or equal to 15 kU/L). Similarly, demographic and baseline characteristics will be summarized by baseline SPT peanut wheal size (less than 8 mm versus greater than or equal to 8 mm).

8.7 Allergy History

Allergy history will be listed by subject. The months since most recent anaphylactic reaction to peanut, and months since most recent reaction to peanut that was treated with therapy (if no therapy for most recent anaphylactic reaction to peanut) will be calculated as the difference between the reported date of the reaction and the informed consent date, in months, using the SAS formula:

INTCK('month', date of reaction, informed consent date, 'C')

The duration of peanut allergy (in months), number of anaphylactic reactions to peanut in lifetime (if any experienced), months since most recent anaphylactic reaction to peanut, and months since most recent reaction to peanut that was treated with a therapy will be summarized continuously by treatment group and overall. Types of other allergic conditions the subject has or has had (whether the subject has experienced anaphylactic reactions to peanuts during his lifetime, the therapies administered for the most recent anaphylactic reaction to peanut, and the symptoms experienced during the most recent peanut exposure) will be summarized categorically by treatment group and overall.

8.8 Diet and Non-Peanut Allergy History

All diet and non-peanut allergy history will be listed by subject. The presence of diet and non-peanut allergy history will also be summarized by treatment group and overall.

8.9 Other Medical History

Medical history will be listed by subject and body system.

8.10 Subject Progress , Unscheduled Visits and Phone Calls

Subject progression through the study will be displayed in a listing of dates for each scheduled study visit. The unscheduled visit listing will include the date of the visit, the reason for the repeat visit (if applicable), and the types of assessments done.

Telephone calls to assess compliance and symptoms, as displayed in Table 3.5, will also be listed by subject.

9 EFFICACY ANALYSES

The ITT Population will be used for summaries and analyses of the efficacy parameters described below. The mITT and PP Populations will be used where indicated.

Screening and Exit DBPCFC food challenge results will be listed by subject and visit, with order (first or second) and date for both the peanut and placebo challenges, and time and presence of dose limiting symptoms listed for each individual dose administered.

The peanut MTD at Screening and Exit DBPCFCs, x-fold increase in peanut MTD, escalation failure status, desensitization response status and subcategory, and response subcategory for missed Exit DBPCFC will be listed by subject. DBPCFCs with indeterminate results, as defined in Section 9.2, will be flagged. Dose levels tolerated will be summarized by time point, dose level, food challenge (peanut or placebo), and randomized treatment group and overall.

9.1 Primary Efficacy Analysis

The primary endpoint is a desensitization response as determined by tolerating at least 300 mg (443 mg cumulative) of peanut protein at the Exit DBPCFC with no more than mild symptoms. Subjects who do not have an Exit DBPCFC will be assigned to a category of responder or non-responder according to Tables 7.1 and 7.2.

The number and percent of subjects with a desensitization response will be reported by treatment group. The desensitization response rate and its 95% confidence interval will be calculated for each treatment group with Wilson (score) confidence limits for the binomial proportion. The 95% confidence interval for the treatment difference (CPNA desensitization rate minus placebo desensitization rate) will be based on Newcombe confidence limits for the difference in binomial proportions. The number and percent of subjects in each response category and subcategory will also be summarized by treatment group.

The primary efficacy analysis will test for a higher desensitization response rate in CPNA versus placebo using the Pearson chi-square statistic in the ITT Population. If any of the expected cell counts are less than 5 (or greater than n-5), Fisher's exact test will be used and exact confidence intervals will be constructed. In this case: (1) exact Clopper Pearson confidence limits will be used for the binomial proportion and (2) exact unconditional confidence limits based on the score statistic will be used for the difference in proportions.

9.2 Additional Analyses of the Primary Efficacy Endpoint

The Exit DBPCFC is defined as indeterminate if the subject was not able to tolerate the placebo challenge up to and including a dose of 600 mg (1043 mg cumulative). Also, prior to Protocol Amendment 3, subjects could be enrolled if they had an indeterminate Screening DBPCFC. The Screening DBPCFC will be considered indeterminate if the subject is not able to tolerate a dose of 100 mg (443 mg cumulative) of the placebo challenge. Subjects with an indeterminate DBPCFC (either at screening or exit) will be excluded for a sensitivity analysis of the primary efficacy analysis in this ITT subset.

The primary efficacy analysis will also be repeated in the mITT and PP populations as sensitivity analyses. These sensitivity analyses effectively assess the results by treating truly missing data as missing-at-random rather than by imputing a response.

9.3 Secondary Efficacy Analyses

All secondary analyses of key secondary endpoints will be performed in the ITT population.

The key secondary efficacy endpoints are:

- Peanut MTD at the Exit DBPCFC
- Change from baseline in the Peanut MTD at the Exit DBPCFC.

These will be tested in a hierarchical order[3,4]. If the primary efficacy analysis is significant at the 0.05 level, then the MTD at Exit DBPCFC will be tested with a Type I error rate of 0.05. If this test is significant, then change from baseline in MTD at the Exit DBPCFC will be tested with a Type I error rate of 0.05. This closed testing procedure maintains the overall Type I error rate at 0.05. If the first test is not significant, the p-value for the change from baseline will be displayed for informational purposes only.

Sensitivity analyses of the key secondary efficacy analyses will be performed by excluding subjects with an indeterminate DBPCFC, as defined in Section 9.2, prior to performing the analyses on the ITT population. Analysis of key secondary endpoints will also be repeated in the mITT and PP populations as sensitivity analyses.

DBPCFC results will be listed at both time points, where applicable, for all randomized subjects. Screening DBPCFC results will be listed for screen failures. Composite results, including MTD and maximum symptom (defined as the most severe of any recorded symptom for that food challenge), will be listed for each DBPCFC for all enrolled subjects, including screen failures. Indeterminate results will be indicated.

The peanut MTD at Screening and Exit DBPCFCs, last dose achieved, number of days at last dose (excluding any time at that dose level prior to an escalation or de-escalation, and excluding any time after an Exit DBPCFC), and whether the subject was an escalation failure (per Tables 7.1 and 7.2) will also be listed. Imputed peanut MTD at the Exit DBPCFC will be flagged. Desensitization response status and response subcategories for missed Exit DBPCFC and desensitization response will also be listed, as described in Section 7.3.

Dose levels administered during DBPCFCs will be summarized by time point and food challenge, by treatment group and overall for the Randomized and ITT populations.

9.3.1 Maximum Tolerated Dose at Exit DBPCFC

The Exit DBPCFC uses a modified PRACTALL dosing regimen. PRACTALL doses are approximately on a logarithmic scale (3 mg, 10 mg, 30 mg, 100 mg, 300 mg). The highest dose level, 600 mg, was chosen in lieu of the 1000 mg dose level from the PRACTALL guidance to further insure safety. Each single PRACTALL dose step corresponds to a 3 to 3.33-fold (roughly 3.16-fold) increase in dose or a 0.477 to 0.523 (roughly 0.5) increase in the $\log_{10}$ scale. The 600 mg dose level is 2-fold increase in dose or approximately a 0.3 increase in the $\log_{10}$ scale above the 300 mg dose. Each increase of 2 PRACTALL dose steps (e.g. 30 to 300 mg or 10 to 100 mg) corresponds to a 10-fold increase in dose or an increase of 1 unit in the $\log_{10}$ scale. Subjects that cannot tolerate the lowest Exit DBPCFC dose will be set to 0.3 mg (a 1 unit decrease from the 3 mg dose, on the $\log_{10}$ scale) for purposes of analysis to allow for the logarithmic transformation. The MTD for the Exit DBPCFC will be imputed using the rules in Section 7.3 for all subjects with a missing Exit DBPCFC.

Estimates for the probability of tolerating each dose or higher will be based on the discrete hazards model with terms for treatment group effect and the MTD at the Screening DBPCFC (baseline) in the $\log_{10}$ scale[2,3]. The extreme value hazard function will be used for the model. The probability estimates will be tabulated by treatment group and adjusted for the MTD at baseline. The adjusted probability estimates will be calculated at the median of the MTD at baseline. The adjusted probability estimates will also be plotted. An unadjusted probability estimate will also be calculated by removing the MTD at baseline term from the model. All subjects in the analysis population are considered eligible for the 1 mg dose. Subjects who did not receive the optional 1 mg dose at the Exit DBPCFC will be considered to have successfully passed that dose level and be eligible for the 3 mg dose level.

The treatment group effect will be assessed using the model with both terms to adjust for the MTD at baseline. The hazard ratio for the treatment group effect with its 95% confidence interval and the p-value will be based on the Wald statistic.

The maximum symptom severity at each dose level, and the cumulative maximum severity at each dose level, will be summarized by treatment group.

9.3.2 Change from Baseline in MTD at Exit DBPCFC

Summary statistics will be reported for Screening DBPCFC (baseline), Exit DBPCFC, and change in MTD for the DBPCFC in the $\log_{10}$ dose scale. Results in the $\log_{10}$ scale will be transformed back to the original scale to also report summary statistics in the original scale. Frequencies and percent of subjects will also be presented for each MTD level at the Screening and Exit DBPCFC. Similarly, frequencies and percent of subjects will be presented for all possible ratios (X-fold increase) of the MTD at the Exit DBPCFC relative to baseline.

Analyses of change from baseline MTD will be performed using change calculated on the $\log_{10}$ scale. An analysis of covariance (ANCOVA) model of change from baseline MTD at Exit DBPCFC ($\log_{10}$ mg) will be fit with terms for treatment group and the MTD at baseline ($\log_{10}$ mg). The baseline adjusted least squares means with 95% confidence intervals by treatment group and for the treatment group difference will be tabulated. The p-value is based on the F-test for treatment group effect adjusted for the MTD at baseline ($\log_{10}$ mg). The ANCOVA model will also be assessed for unequal slopes by adding a term for the treatment group by baseline interaction and using an F-test to test for unequal slopes. If there is a signal of unequal slopes at the 0.10 significance level, then the least squares means with 95% confidence interval, and p-value for the F-test of the treatment group difference will be calculated and reported at baseline MTDs of 1 mg, 3 mg, 10 mg, and 30 mg. P-values and confidence intervals are based on the normality assumption. Residuals for ANCOVA will be assessed for non-normality using the Shapiro-Wilk test. If significant at the 0.05 level, then the Wilcoxon rank sum statistic will be used to test for a treatment group difference to examine the robustness of the ANCOVA F-test. Further exploration may be warranted if unequal slopes are noted.

Least squares mean statistics (point estimates and confidence intervals) from the ANCOVA analysis of change from baseline analysis in the $\log_{10}$ scale will be transformed back to the original scale to obtain geometric least squares mean statistics by treatment group of the ratio of the MTD at the Exit DBPCFC to baseline.

9.3.3 IgE and IgG4

Blood samples to measure peanut IgE and peanut-specific IgG4 levels, and total IgE levels will be collected prior to the Screening DBPCFC and prior to the Exit DBPCFC. Peanut-specific IgE/IgG4 ratio will be calculated, listed by subject, and summarized by visit and treatment group. Results outside the limits of quantification will be displayed as less than the lower limit of quantification (LLOQ), or greater than the upper limit of quantification (ULOQ), as appropriate. These values will be summarized as either the LLOQ, or the ULOQ. If the peanut IgE or peanut-specific IgG4 is outside of the limits of quantification, the IgE/IgG4 ratio will be calculated using the LLOQ or ULOQ as appropriate.

Results will be provided by a central laboratory and summarized by visit and treatment group, using the geometric mean and standard deviation in lieu of arithmetic mean and standard deviation. 95% confidence intervals, based on the geometric calculations, will also be provided. Ratios of post-baseline visit to baseline and ratio of those ratios of treatment groups, where applicable, will be presented similarly. All results will be displayed for the ITT population.

9.3.4 Skin Prick Test

Results from the Skin Prick Test (SPT) will be listed, including test date, timing of test reading (10, 15 minutes), and measurements (mm) of the following hive/wheals: peanut wheal, peanut erythema/flare, saline wheal, saline-glycerin

erythema/flare, histamine wheal, and histamine erythema/ flare. The summary will incorporate 95% confidence intervals and will include observed values at both 10 and 15 minute time intervals, as well as the maximum observed value for either time interval, with change from baseline and difference in change from baseline between treatment groups where applicable, by treatment group, visit, and hive/wheal type for the ITT population.

9.4 Immune Tolerance Network (ITN) Samples

Optional blood samples are collected for exploratory analysis by the Immune Tolerance Network. These analyses are will be conducted separately and are outside the scope of this analysis plan. Sample collection dates and times are listed by subject and time point.

9.5 Exploratory Efficacy Analysis

The influence of site and other potentially prognostic baseline factors on treatment group differences in the desensitization response rate and MTD at Exit DBPCFC will be explored using the ITT population.

The factors to be explored will be:

- MTD of peanut protein at Screening DBPCFC, in log10 scale
- Age
- Presence of asthma, as recorded as part of allergy history
- Presence of allergic rhinitis or hay fever, as recorded as part of allergy history
- History of allergy to a food other than peanut, as recorded as part of the diet and non-peanut allergy history
- Severity of the peanut allergy, defined as the number of anaphylactic reactions to peanut experienced, divided by the duration of the peanut allergy, and categorized into: subjects with 0 anaphylactic reactions, those with at least one reaction but less than 1 every 5 years, and those with more than 1 reaction every 5 years
- Duration of peanut allergy in months, as recorded as part of allergy history
- Study site
- Peanut IgE level at baseline, in log10 scale
- Maximum SPT peanut wheal diameter at baseline
- VAS score at baseline
- BMI at baseline

If necessary, categorical variables will be pooled such that each pooled level will have at least 3 observations for each treatment group.

For nominal categorical variables, pooling will start with the smallest level which will be pooled with the next larger level until each pooled level has 3 observations for

each treatment group. For ordinal categorical variables, pooling will proceed in the same manner but will start with the minimum ordinal value and pool in ascending order. Ties will be broken by sorting (in ascending order) the desensitization rate for CPNA, then by the desensitization rate for placebo, then by the geometric mean of the MTD for CPNA, and then by the geometric mean of the MTD for placebo. If the tie is still not broken, then tied levels (that are subject to pooling) are pooled together as the initial step.

If model parameters for a categorical variable are not estimable, then the minimum number of observations of 3 observations per pooled level for each treatment group will be increased by 1 in the above pooling algorithm until the model parameters are estimable. If the model parameters for a binary categorical variable are not estimable, then that factor will not be explored for its effect.

9.5.1 Effect on Desensitization Response Rate

The influence of these factors on treatment group differences in the desensitization response rate will be explored using logistic regression. These analyses will be performed on the ITT population.

The logistic regression model will include terms for treatment group and the baseline factor to be explored (e.g. site), and an interaction term between the baseline factor with treatment group. The odds ratio for the treatment group effect will be calculated at each level for categorical variables. The odds ratio for the treatment group effect will be calculated at 3 values for continuous variables (the 25% percentile, median, and 75% percentile). Main effects for treatment group and the baseline factor will also be calculated after dropping the interaction term from the model. A 95% confidence interval and p-value will be presented for each odds ratio using the Wald statistic. The p-value for the interaction term will also be presented and based on the Wald statistic.

9.5.2 Effect on Maximum Tolerated Dose at Exit DBPCFC

Each baseline factor, other than peanut MTD at Screening DBPCFC (since it is already included as a covariate) will independently be evaluated using the discrete hazards model described in Section 9.3.1. Terms for treatment, MTD of peanut protein at the Screening DBPCFC in the log10 scale, the baseline factor to be explored (e.g. site), and an interaction term between the baseline factor with treatment will be included. The hazard ratio for the treatment effect will be calculated at each level for categorical variables. The hazard ratio for the treatment effect will be calculated at 3 values for continuous variables (the 25% percentile, median, and 75% percentile). Main effects for treatment and the baseline factor will also be calculated after dropping the interaction term from the model. A 95% confidence interval and p-value will be presented for each hazard ratio using the Wald statistic. The p-value for the interaction term will also be presented and based on the Wald statistic.

9.6 Interim Analysis

There is no interim analysis of efficacy planned for this study.

9.7 Data Monitoring Committee

The DMC will meet regularly to review safety data, as described in the DMC Charter.

10 SAFETY ANALYSES

Unless otherwise noted, the Safety population will be used for all summaries of safety parameters. Safety listings will include all subjects in the Enrolled population, sorted by treatment received (CPNA then PBO), with subjects who did not receive any study product (NONE) at the end of the listing.

10.1 Study Treatment Exposure

Randomized study treatment is administered both in-clinic (for escalation dosing) and at home. Food product administered at a DBPCFC is not considered randomized study treatment.

Subjects receive randomized study treatment at Visit 01 and regularly scheduled Up-dosing Visits as described in Section 3.2.2. All randomized study treatment, whether for in-clinic or at home use, will be dispensed from the unblinded pharmacist or dietician, and be recorded using the dispensing record in TEMPO. Each bottle of randomized treatment dispensed will also be tracked with a treatment returned record in TEMPO, even if 0 capsules were returned. Most visits will include both a dispense record for a small number of capsules for the in-clinic up-dosing, and a subsequent dispense record for the entire amount of capsules given to the subject for at-home use, both on the same day. Therefore, dispense and return records will be matched by sorting both sets of records by subject, date, and capsule quantity.

If subjects return a bottle at a later visit, it will be assumed that the capsules were ingested during the time period for which it was initially dispensed. These return records will be matched to the correct dispense record using a combination of amounts of capsules returned, date returned, and the date dispensed.

If a subject does not return a bottle, the reason not returned (lost, destroyed, and other) will be recorded and numbers of capsules returned will be missing.

The average dose per day during each nominal dosing period (e.g., the 3 mg dosing time period, the 6 mg dosing time period, etc.) will be calculated as the total dose consumed during that period, divided by the number of days at that dose (defined as last date - first date + 1, for that period). First and last dose dates for each period will be determined based on a combination of in-clinic dosing (occurring on the day that study product was dispensed) and the dosing diary entries occurring

on or after the date that study product was dispensed for that period, and on or before the date that study product was returned. Any study product taken after Exit DBPCFC will be excluded from these calculations. Specifically:

- If the nominal dosing period begins with in-clinic dosing, such as for a dose escalation, the first dose date will be the dose date recorded on the in-clinic dosing CRF page, and the last dose date will be the last dose date recorded in the dosing diary prior to a dose change (if present), prior to an Exit DBPCFC (if no further dose changes are present), or prior to the end of the study (if no further dose changes are present and an Exit DBPCFC is not performed).

- If the nominal dosing period does not begin with in-clinic dosing, the first dose date will be the earliest dose date recorded in the dosing diary, after the date on which that dose of study product was dispensed.

If a subject titrates to a higher dose then is decreased back to an earlier dose, the average daily doses for the two periods at that dose level will be listed separately but combined for summaries. The combined average daily dose will be calculated as the total dose for both periods, divided by the total number of days across both periods. If a subject has 3 or more distinct time periods at the same dose level, they will be presented similarly.

The duration of treatment will be calculated as (date of last randomized study treatment administration– date of first randomized study treatment + 1). The duration of treatment in weeks will be calculated as the duration of treatment in days, divided by 7.

The overall duration of treatment, in weeks, will be summarized continuously by treatment. The overall treatment duration, in days, will be summarized by 30 day increments: ≤ 30 days, 31 – 60 days, … 241 – 270 days, and >270 days. Duration will be listed by subject in both weeks and days.

The maximum dose achieved will be listed, and summarized both continuously and categorically by treatment group. The categorical summary will display the number of subjects whose highest dose is 0.5, 1, 1.5, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, or 300 mg/day. The last dose achieved, defined as the assigned dosage from the last bottle dispensed prior to Exit DBPCFC, will be listed and summarized similarly.

A dose escalation will be identified as a subject consuming an increased dose from the previous dose. An unsuccessful dose escalation will be defined as a subject consuming an increased dose, followed by a dose reduction. Dosing with incorrect study product will not be counted as a dose escalation nor will it be counted as an unsuccessful dose escalation. The numbers of dose escalations, unsuccessful dose escalations, dosing with incorrect study product, and dose reductions, will be listed and summarized by treatment group.

In-clinic dosing, including visit , date and time, dose level, whether it was a dose reduction (and reason), and whether the dose was tolerated will be listed by subject.

To evaluate the time-course of tolerated up-dosing, the number and percent of subjects on each dose (0.5, 1, 1.5, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, or 300 mg/day) will be summarized at the End of Visit 1 and then for every 2 weeks beginning with Week 2 (Day 14), by treatment group, and presented using boxplots.

At-home dosing compliance will also be listed and summarized. Daily diary records, including date and time, whether a full or partial dose was consumed (or the dose was missed), reason for partial or missed dose will be listed. If any dose-related symptoms are present, the symptoms, onset time, and resolution time will also be listed.

The number of days of planned at-home dosing, calculated as the number of days on study minus the number of days of in-clinic dosing, will be listed by subject. For each subject, the number and percent of days for each type of dose (full dose, partial dose, and missed dose) where the percent is calculated as the number of days for that type of dose divided by the number of days of planned at-home dosing, will be listed. The number and % of days with dose-related symptoms, as recorded in the daily diary, will also be listed for each subject.

The number of days with planned at-home dosing will be summarized by treatment group and overall. The percentage of days of planned at-home dosing on which any at-home dose (i.e., full or partial) was consumed, a full dose was consumed, a partial dose was consumed, a dose was missed, or days with dosing symptoms will be summarized similarly.

10.2 Prior and Concomitant Medications and Therapies

All medications recorded on the Concomitant Medications CRF page will be coded using the World Health Organization drug dictionary (WHODRUG), March 2013 version. Medications will be listed and summarized by Anatomical Therapeutic Chemical (ATC) Level 1 and Preferred Name.

Prior medications are defined as those which are only taken prior to the beginning of the active treatment period. Concomitant medications are medications taken at any time during the active treatment period, or those which are able to be taken during that period. Any medications recorded which begin after the last dose of randomized study treatment will also be classified as concomitant medications. As needed (*PRN*) medications, which may not be taken for long periods of time but which are prescribed to the subject, and the prescription period overlaps with the active treatment period, will be considered concomitant medications.

All non-study medications will be listed by subject. Rescue medications and medications prescribed as a result of an anaphylactic reaction will be listed by subject. Further presentation of epinephrine use data is described in Section 11.1.

Concomitant medications will be summarized by treatment group and overall. Subjects will be counted no more than one time per Preferred Name and no more than 1 time per ATC Level 1 in the summary. A similar summary will be presented for concomitant medications marked as rescue medications.

Concomitant non-drug therapies will be similarly listed by subject.

10.3 Adverse Events

All reported adverse events (AEs) will be classified into System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. A summary of SOC, PT, and verbatim term will be provided.

Treatment-emergent adverse events (TEAEs) are defined as any event starting during or after the active treatment period. Any event occurring on the same day as a DBPCFC or in-clinic escalation dosing will be considered to be associated with those events, and flagged as such in the listings. Events will be classified by onset time with regards to time of last dose (within 2 hours of last dose, > 2 hours since last dose, and unknown time since last dose).

Events will be further classified by time period of onset, as follows:

- *Pre-study*: All events beginning prior to first dose of Screening DBPCFC; if times are unavailable, any event prior to the first day of Screening DBPCFC.
- *Screening DBPCFC*: All events beginning after the first dose of the food challenge during the Screening DBPCFC, and within 24 hours of the last dose of that food challenge and prior to the first dose of randomized treatment. If times are not available, any event starting on the same day as any part of the Screening DBPCFC will be categorized as Screening DBPCFC.
- *Pre-treatment*: All events beginning more than 24 hours after the last dose of the Screening DBPCFC but before the first dose of randomized treatment. If the two halves of the food challenge are more than 24 hours apart, events that begin more than 24 hours after the end of the first half, but prior to the start of the second half, will be categorized as Pre-treatment. If times are not present, events beginning on any day after the first day of Screening DBPCFC, and before Visit 01 Day 1, excluding any day on which Screening DBPCFC is administered, will be Pre-treatment.
- *Visit 01*: All events beginning on or after the first dose on Visit 01 Day 1, and within 24 hours of the last dose administered at Visit 01 (Days 1, 2, or 3); if times not present, events beginning on the same date as any day of Visit 01.
- *Up-dosing Visit*: All events beginning on or after the increased dose administered and within 24 hours of that dose; if times not present, events

beginning on the same date as a dose increase. If the same dose level, or a decreased dose level, is administered at a scheduled up-dosing visit, an event within 24 hours of that dose or on that day will be classified as On-treatment, unless there had been a higher dose administered within that 24 hour period or on that day, respectively.

- *On-treatment*: All other events beginning after the first dose of randomized treatment and prior to the Exit DBPCFC, or within 24 hours of the last dose of randomized study treatment if an Exit DBPCFC is not performed or is >24 hours after the last dose. If times are not available, any event starting during the active treatment period, but not on the same day as Visit 01 or an Up-dosing visit, will be On-treatment.
- *Exit DBPCFC*: All events beginning after the first dose of product was administered during the Exit DBPCFC, and within 24 hours of the last dose of that food challenge. If times are not available, any event starting on the same day as any part of the Exit DBPCFC will be categorized as Exit DBPCFC.
- *Post-Exit DBPCFC*: All events beginning more than 24 hours after the Exit DBPCFC. If the two halves of a food challenge are more than 24 hours apart, events that begin more than 24 hours after the end of the first half, but prior to the start of the second half, will be categorized as Post-Exit DBPCFC.
- *Post-treatment*: All events beginning >24 hours after the last dose and prior to the Exit DBPCFC if an Exit DBPCFC is performed, or >24 hours after the last dose if an Exit DBPCFC is not performed. If times are not available, all events beginning on or after the day after the last part of the Exit DBPCFC (if performed) or the day after the last dose of randomized treatment (if no Exit DBPCFC performed) will be categorized as Post-treatment. If the two halves of the Exit DBPCFC are more than 24 hours apart, events that begin more than 24 hours after the end of the first half, but prior to the start of the second half, will be categorized as Post-treatment.

Listings will be provided for all adverse events; serious adverse events (SAEs); severe, life-threatening, or fatal adverse events; adverse events leading to death; adverse events leading to permanent withdrawal of study treatment; adverse events related to study treatment; and adverse events occurring within 2 hours of the last dose of randomized study treatment. Listings of both adverse events associated with DBPCFC, and SAEs associated with DBPCFC, will be provided. A separate listing of all adverse events, sorted by time period of onset, will also be provided; and SAEs will be flagged.

An overall summary of frequencies of types of adverse events (TEAEs, SAEs, etc.) will be provided. An additional summary table of all TEAEs by Preferred Term, in order of descending frequency, will also be provided.

Summaries of adverse events by time period, SOC, and PT will be provided for TEAEs, treatment-emergent SAEs, and TEAEs related to study treatment. Subjects will be counted at most one time per time period overall, at most one time per SOC and at most one time per PT for these summaries. Summary tables will be sorted in order of time period (overall, then chronological), descending overall frequency

of SOC and PT, with alphabetical sorting for ties. The number of subjects at risk for each time period (i.e., the number of subjects on study at the beginning of each time period) will be used as the denominator. In other words, the number of subjects in the Safety population will be used as the denominator for the Overall, On-treatment, and Post-Treatment time periods, the number of subjects undergoing Visit 01 will be used as the denominator for Visit 01, the number of subjects with 1+ updosing visits will be used as the denominator for Updosing Visit, the number of subjects undergoing the Exit DBPCFC will be used as the denominator for the Exit DBPCFC, Post-Exit DBPCFC time points.

Events related to study treatment are defined as those classified as possibly, probably, or definitely related to study treatment. If relationship is missing, the event will be conservatively be summarized as being related to study treatment.

Event severity is classified as mild, moderate, severe, life-threatening, or death. If severity is missing, a separate category of missing severity will be included in the summary table, and no imputation of severity will be performed.

An additional summary of TEAEs by time period, SOC, and PT will be presented by start time of the adverse event relative to last dose (within 2 hours; > 2 hours; and unknown, where the event start time or time of last dose is unknown). TEAEs will also be summarized by time period SOC, PT, and severity. Subjects will be counted at most one time per SOC and at most one time per PT, at the maximum reported severity. If severity is missing, the subject will be summarized as having the highest possible severity.

10.4 Food Allergy Episodes

The occurrence of a safety event associated with accidental food ingestion will be reported as a food allergy episode, as per Section 7.2 of the protocol. Any such event that meets the definition of an SAE will also be reported as an adverse event. All reported food allergy episodes will be listed by subject. Episodes of allergic reaction associated with foods other than peanut (as determined prior to database lock, as described in Section 12) will be flagged.

The number of subjects experiencing any food allergy episode, the number of subjects experiencing a food allergy episode in response to peanut, the number of episodes of each (peanut-related and non-peanut related) experienced per subject, and the total number of food allergy episodes will be summarized. The number of episodes with unscheduled clinic visits, treatment administered, or considered SAEs will also be summarized.

The rate of food allergies and those with unscheduled clinic visits, treatments administered, or considered SAEs will be calculated by dividing the total numbers of events by the number of subjects in that treatment group. These rates will similarly be summarized by randomized treatment group and overall.

10.5 Symptoms During DBPCFC

During each food challenge, the severity of pre-specified symptoms (hives, throat tightness, throat swelling, throat discomfort, hoarseness, laryngeal edema, skin flushing, pruritus, rhinorrhea, sneezing, nasal congestion, cough, wheezing, dyspnea, abnormal pain, abdominal cramping, nausea, vomiting) is rated as none, mild, moderate, severe, or life-threatening at each dose level of each food product. In addition, the presence of dose-limiting symptoms is recorded.

Symptoms at the Screening and Exit DBPCFCs will be listed by subject.

Symptoms will be summarized separately for symptoms during Screening DBPCFC (separately for the Safety and Screening DBPCFC Only populations) and Exit DBPCFC (for the Safety population). Subjects will be counted at most one time per symptom for each summary, at the most severe level recorded for that subject. The maximum dose severity of any symptom, and the presence of any dose limiting symptoms, will also be summarized.

10.6 Symptoms During Escalation Dosing

During each escalation dosing, the severity of pre-specified symptoms is similarly rated as none, mild, moderate, severe, or life-threatening. In addition, the presence of dose-limiting symptoms and whether the dose was tolerated is recorded for each escalation dose.

Symptoms will be listed by subject, time point, and dose level. Maximum severity by symptom, maximum overall severity, and presence of any dose limiting symptoms will be summarized across all dose levels. Symptoms, maximum severity of any symptom, presence of dose limiting symptoms, and whether the dose was tolerated will be summarized for each dose level. If a subject is administered the same dose at more than 1 up-dosing visit (either the subject remained at the same dose as the previous visit, or a subject had a prior dose increase and subsequent dose reduction), the most severe symptoms and dose-limiting symptoms will be summarized for that dose level.

10.7 Symptoms During At-Home Dosing

A description of at-home dosing symptoms, and their onset and resolution times, will be collected in the daily diary and listed by subject and date. The number of days with any at-home dosing symptom will be listed by subject and summarized by treatment group.

10.8 Pregnancy Test Results

Pregnancy test results will be listed by subject and visit.

10.9 Spirometry and PEFR

Spirometry (forced expiratory volume, FEV1) and/or Peak Expiratory Flow Rate (PEFR) assessments are performed prior to any DBPCFC. PEFR is also performed at each up-dosing visit. Three attempts of FEV1 are performed, and the best (highest) value flagged in data listings. Similarly, three attempts of PEFR are performed, and the best (highest) value flagged in data listings. Only the best FEV1 value and the best PEFR value will be summarized.

Forced vital capacity (FVC), predicted FVC, predicted FEV1, predicted FEV1/FVC are also listed, and both results and changes from baseline summarized by treatment group and overall for the Safety population. PEFR is listed and summarized similarly.

10.10 Vital Signs

BMI will be calculated as (weight in kilograms)/ (height in meters)^2.

Vital signs (pulse rate, systolic/diastolic blood pressure, body temperature, height, BMI, and weight) will be listed by subject and visit. Observed values and change from baseline will be summarized by visit and treatment group.

10.11 Physical Examination

Physical examination results will be listed by subject and visit. Results will be summarized by body system and visit. A shift table of changes from baseline to each post-baseline visit, plus to the worst post-baseline visit, within treatment group and body system will also be provided.

The worst post-baseline result will be defined, within body system, as:

- Abnormal, if any abnormal result is present after the first dose of randomized study treatment
- Normal, if all non-missing results after the first dose of treatment are normal
- Not Done, if no results are present after the first dose of treatment

10.12 Physician Global Assessment

A 100-mm VAS will be used by the investigators to assess overall disease activity as a marker for safety (0 = no disease activity, 100 = very severe disease activity). VAS scores will be listed by subject and date. Observed values and changes from baseline will be summarized by treatment group and visit for the Safety population. Summary statistics will include 95% confidence intervals for point estimates of the mean. The treatment difference in mean changes from baseline with 95% confidence intervals will also be summarized.

11 EXPLORATORY ANALYSES

11.1 Epinephrine Use as Rescue Medication

Epinephrine use is defined as any rescue medication with a preferred name of 'EPINEPHRINE' when coded as described in Section 10.2, and with documentation of administration to a subject on a specific date.

All subjects, per protocol, are required to have epinephrine autoinjectors for use in case of a suspected anaphylactic reaction occurring outside of the clinic. There are, however, differences in how, and even if, physicians record the prescription of epinephrine autoinjectors for as-needed (PRN) use. As a consequence of this, the presence or absence of a PRN prescription for epinephrine cannot be taken to indicate epinephrine usage, regardless of whether the prescription was written prior to, or after, enrollment in the study. What is important is to be able to quantitate the number of subjects receiving doses of epinephrine and the number of doses. As epinephrine should only be administered to treat a discrete allergic reaction, each dose of epinephrine should be closely temporally associated with a specific safety event. In cases where a PRN epinephrine prescription is issued after the start of study-product dosing, the sites are queried as to if, and when, epinephrine was actually administered and to treat what specific event.

Epinephrine use will be categorized by the following time points, based on epinephrine use on the same day(s) as any of the following events:

- Any use on the same date as an accidental exposure (defined as a recorded food allergy episode) occurring on or after the first dosing date of randomized treatment
- Screening DBPCFC, further categorized into
    - Peanut Challenge: if epinephrine is administered on the day of a peanut challenge, the default assumption will be that the epinephrine administration was in response to a peanut-related event, regardless of whether a placebo challenge was also conducted on the same day)
    - Placebo Challenge
- Post Screening DBPCFC, Prior to Randomized Study Treatment
- Visit 01 (including all days of that visit)
- Up-dosing Visit (including any day in which dose is increased)
- On-Treatment (any day during the active treatment period, excluding Visit 01 and Up-dosing Visits)
- Exit DBPCFC, further categorized into
    - Peanut Challenge (with same provisos as for Screening DBPCFC)
    - Placebo Challenge
- Post Treatment or Post Exit DBPCFC (any day after the Exit DBPCFC, if administered, or the day after the last dosing date of randomized study treatment)

As described in Section 10.3, if a subject undergoes an Up-dosing visit but the dose stays the same or decreases, that day will be classified as On Treatment. If both

peanut and placebo DBPCFCs were on the same date (either at Screening or Exit), any epinephrine use on that date will be categorized as used for the peanut challenge.

Frequency of use will be summarized overall (for any frequency) and by frequency administered (Once, twice, etc.). The number of subjects at risk at each timepoint will be used as the denominators; for instance, only subjects undergoing Exit DBPCFC will be used as the denominator for epinephrine use during Exit DBPCFC. Summaries will be presented separately for the Safety and Screening DBPCFC Only populations.

11.2 Summary of Rescue Medications

Non-study medications used during the course of the study may be recorded on CRF pages other than the Concomitant Medications CRF page. Information about epinephrine and other rescue medications and their frequency of use, will be consolidated and summarized for use in the clinical study report (CSR). A table shell will be finalized prior to database lock but not included in the SAP.

11.3 Anaphylaxis Episodes

All reported anaphylactic reaction episodes will be listed by subject. The number of subjects experiencing such a reaction, the number of reactions per subject, and the total number of reactions reported will be summarized. Episodes will also be summarized by the episode trigger.

These summaries will be repeated for:

- Episodes where epinephrine is administered on the same date (based on the Concomitant Medication CRF pages)
- Episodes where epinephrine is not administered on the same date
- Episodes which occur on the same date as accidental exposure to a food allergen
- Episodes which do not occur on the same date as accidental exposure to a food allergen

These summaries will be produced separately for the Safety and Screening DBPCFC Only populations.

11.4 Imputation of MTD as Maximum CPNA Dose

Subjects who do not undergo the Exit DBPCFC have the MTD for the Exit DBPCFC imputed as the MTD at the Screening DBPCFC, as described in Section 7.3. As an exploratory analysis, subjects randomized to CPNA who do not undergo the Exit DBPCFC will have their MTD for the Exit DBPCFC imputed as the higher of the Screening DBPCFC MTD or the highest tolerated dose of randomized study treatment tolerated during up-dosing. The highest tolerated dose is defined as the highest dose level taken for at least two weeks, which is not immediately followed by a dose reduction or withdrawal from the study.

The MTDs at the Exit DBPCFC will be summarized for the CPNA treatment group with and without this imputation scheme.

12 PRE-DATABASE LOCK DATA DETERMINATION

The purpose of the pre-database lock blinded data review is the assignment of subjects to their appropriate study populations (ITT, mITT, PP), the classification of their responder status (Responder or Non-responder), and the designation of their response subcategory (for Responders - Passed Exit DBPCFC or *Ad libitum* peanut consumption; for Non-responders - Failed Exit DBPCFC, Reached 300 mg/day but Exit DBPCFC was not conducted, or Escalation Failure). The following items (listed below) will be finalized based on blinded data review, prior to database lock and unblinding. This blinded data review will be performed by study personnel who are blinded to all subject treatment assignments, as described in Section 7.7. The team involved in making these determinations and final index of listings reviewed by the team will be documented. Each of the items will be finalized and documented prior to database lock.

- Protocol violations, as described in Section 7.5, will be classified as major violations or minor violations.

- List of exclusions from analysis populations as described in Section 5. All subjects who were randomized but not included in 1 or more analysis populations (other than the Enrolled and Screening DBPCFC Only populations) will be reviewed.

- Responder status, as described in Section 6.10, will be reviewed and compared to disposition information (reasons for early discontinuation and reasons Exit DBPCFC not done), protocol violations, and adverse events to ensure correct classifications. Overall responder status, response subcategory, and reason for missing Exit DBPCFC, as described in Sections 6.9 and 6.10, will be finalized.

- Subjects who have added *ad libitum* peanut consumption to their diet and also had additional reasons for missing the Exit DBPCFC will have imputation rules for MTD of peanut determined on a case-by-case basis. If any subjects meet these criteria, the imputation rules and justification will be documented.

- Food allergy episodes will be reviewed and categorized as peanut-related or non-peanut related.

The listings displayed in Table 11.1 will be provided for the blinded data review, with randomized treatment group and subject identifiers masked as described in Section 6.13.

Table 11.1

Listing	Title
16.2.1.1	Subject Disposition
16.2.2	Protocol Deviations
16.2.3	Analysis Populations
16.2.5.1	Composite Dosing Information for Randomized Study Treatment
16.2.5.6	Screening and Exit Double-Blind Placebo-Controlled Food Challenge Results
16.2.5.7	Exit DBPCFC Maximum Tolerated Dose, Escalation Failure, and Responder Classification
16.2.7.9	Food Allergy Episodes

In those listings, the following variables will also be redacted (displayed as 'XXX' or similar):

- Dates of randomization, first and last doses, last study visit, discontinuation/termination in disposition listing
- Dose dates and times in composite dosing information
- Dates and times in food challenge result listing.

The lead statistician, sponsor statistician, or blind data review personnel may request additional masked listings be prepared for the review.

Prior to conducting the blinded data review, the relevant data listings (above) will be thoroughly QC'd against related listings with subject numbers masked by a randomly created subject identifier, as described in Section 7.7. Related listings will include, at a minimum, listings pertaining to inclusion/exclusion protocol deviations (Listing 16.2.1.4), dosing (Listings 16.2.5.3, 16.2.5.4), AEs (Listings 16.2.7.1, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.8, 16.2.7.9, 16.2.7.10) and rescue interventions (Listings 16.2.9.2, 16.2.9.3, 16.2.9.4, 16.2.9.5). The QC of the masked data listings will be conducted by the sponsor statistician, who will not otherwise participate in the blinded data review.

13 REFERENCES

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14 ATTACHMENTS

14.1 Table of Contents for Data Displays

14.1.1 Tables

Number	Title	Population
14.2.15	Change from Baseline in Maximum Tolerated Dose at Exit DBPCFC	ITT Excluding Subjects with Indeterminate Exit DBPCFC
14.2.16	Change from Baseline in Maximum Tolerated Dose at Exit DBPCFC	mITT
14.2.17	Change from Baseline in Maximum Tolerated Dose at Exit DBPCFC	PP
14.2.18	Summary of Maximum Symptom Severity by Dose at Exit DBPCFC	ITT
14.2.19	Analysis of the Effect of Baseline Factors on Desensitization Response	ITT
14.2.20	Analysis of the Effect of Baseline Factors on the Probability of Tolerating Each Exit DBPCFC Dose L	ITT
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14.2.23	Summary of Skin Prick Test	ITT
14.3.1.1	Overall Summary of Adverse Events	Safety
14.3.1.2	Summary of Treatment-Emergent Adverse Events by Time Period	Safety
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14.3.8.3	Summary of Epinephrine Rescue Medication Use by Frequency of Use and Time Point	Safety

Number	Title	Population
14.3.8.4	Summary of Epinephrine Rescue Medication Use by Frequency of Use and Time Point	Screening DBPCFC Only

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Number	Title	Population
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14.2.24	Probability of Tolerating Each Exit DBPCFC Dose Level or Higher (Based on the Discrete Hazards Model)	ITT Excluding Subjects with Indeterminate Exit DBPCFC
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14.1.3 Listings

Number	Title	Population
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16.2.1.3	Randomization Status	Enrolled
16.2.1.4	Inclusion/Exclusion Deviations	Enrolled
16.2.2	Protocol Deviations	Enrolled
16.2.3	Analysis Populations	Enrolled
16.2.4.1	Demographics and Baseline Characteristics	Enrolled
16.2.4.2	Medical History	Enrolled
16.2.4.3	Allergy History	Enrolled
16.2.4.4	Diet and Non-Peanut Allergy History	Enrolled
16.2.4.5	Scheduled Subject Visits	Enrolled
16.2.4.6	Unscheduled Visits	Enrolled
16.2.4.7	Phone Calls	Enrolled
16.2.5.1	Composite Dosing Information for Randomized Study Treatment	Enrolled
16.2.5.2	Randomized Study Treatment Dispensing and Return Records	Enrolled
16.2.5.3	In-Clinic Dosing	Enrolled
16.2.5.4	Daily Diary Record	Enrolled
16.2.5.5	Composite Daily Diary Dosing Information	Enrolled
16.2.5.6	Screening and Exit Double-Blind Placebo-Controlled Food Challenge Results	Enrolled

Number	Title	Population
16.2.5.7	Exit DBPCFC Maximum Tolerated Dose, Escalation Failure, and Responder Classification	Enrolled
Efficacy		
16.2.6.1	IgG and IgE Test Results	Enrolled
16.2.6.2	Skin Prick Test	Enrolled
16.2.6.3	Exploratory ITN Samples Collected	Enrolled
Safety		
16.2.7.1	Adverse Events	Enrolled
16.2.7.2	Adverse Events by Timepoint	Enrolled
16.2.7.3	Serious Adverse Events	Enrolled
16.2.7.4	Severe, Life-Threatening, or Fatal Adverse Events	Enrolled
16.2.7.5	Adverse Events Leading to Death	Enrolled
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16.2.7.7	Adverse Events Associated with DBPCFC	Enrolled
16.2.7.8	Serious Adverse Events Associated with DBPCFC	Enrolled
16.2.7.9	Food Allergy Episodes	Enrolled
16.2.7.10	Screening Double-Blind Placebo-Controlled Food Challenge Symptoms	Enrolled
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16.2.8.3	Peak Expiratory Flow Rate	Enrolled
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16.2.8.6	Physicians Global Assessment of Overall Disease Activity	Enrolled
16.2.9.1	Non-Study Medications	Enrolled
16.2.9.2	Rescue Medications	Enrolled
16.2.9.3	Medications Prescribed As a Result of an Anaphylactic Reaction	Enrolled
16.2.9.4	Rescue Medication: Epinephrine Usage	Enrolled
16.2.9.5	Non-Drug Therapies	Enrolled
16.2.10	Anaphylaxis Episodes	Enrolled

DOCUMENT:	Statistical Analysis Plan
PROTOCOL:	ARC001
	Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Oral Immunotherapy (OIT)
SAP VERSION:	**Addendum to** Final v1.1
ADDENDUM DATE:	06 February 2015
PROTOCOL DATE:	14 May 2014 (Amendment 3)
SPONSOR:	Allergen Research Corporation
PREPARED BY:	Clinipace Worldwide
AUTHORS:	**Venita DePuy, PhD**

APPROVAL SIGNATURES

SIGNATURE: DATE:

9 FEB '15

Robert Elfont, MD, PhD
Chief Medical Officer
Allergen Research Corp.

10 FEB 2015

Ron Marks, PhD
Chief Scientific Officer
Clinipace Worldwide

1 INTRODUCTION

This document serves as an addendum to the finalized Statistical Analysis Plan. It describes minor additions to the analyses, and clarifies aspects of the earlier text.

2 CHANGES TO THE SPECIFIED ANALYSES

The following changes will be made:

2.1 Adverse Event Classification

Adverse events will be classified using MedDRA v16.0 in conjunction with investigator evaluation of the etiology of the adverse event. Each event will be classified as one of the following:

- Symptom of allergic reaction (allergy)
- Symptom of allergic reaction to food (food allergy)
- Non-allergic symptom, alternate etiology known
- Non-allergic symptom, alternate etiology not known
- Unable to classify symptoms as either allergic or non-allergic.

Flags for each of those classifications will be added to the AE listings.

Events classified as allergies or food allergies will be classified as having system organ class (SOC) = 'IMMUNE SYSTEM DISORDERS', preferred term (PT) = 'HYPERSENSITIVITY', and lower level term = 'ALLERGIC REACTION'. Those events will be further classified by specific system organ class and preferred term of the allergy (for instance, vomiting would have specific SOC = 'GASTROINTESTINAL DISORDERS' and PT='VOMITING', as per MedDRA).

In addition to the original summary tables, additional summary tables of hypersensitivity adverse events, by specific classification, will be presented.

Table and listing footnotes will be updated as appropriate.

2.2 Completer Population

An additional analysis population will be added. The Completer population will include all subjects in the mITT population who were eligible for the Exit DBPCFC. Exclusions from this analysis population will be reviewed at the pre-DBL determination meeting as described in Section 12 of the SAP.

Efficacy tables currently being produced on the ITT, mITT, and PP populations will also be produced on the Completer population.

2.3 Study Product Administered After Exit DBPCFC

In some cases, study product was administered following Exit DBPCFC, to allow subjects to continue to receive product prior to rolling over to the ARC002 study. Subjects remained enrolled in the ARC001 study during this time, and recorded study product in the daily diary.

This post-Exit DBPCFC study product will be excluded from summaries of exposure and compliance, and footnoted as such. Disposition listings reflecting the date of last study treatment will be flagged to indicate where study treatment was taken after Exit DBPCFC.

2.4 Clarifications to original text

- An unsuccessful dose increase is defined as a single dose at a higher dose level, followed by a return to the previous dose level (or a lower level).

- A dose reduction is any decrease in dose level that does not qualify as an unsuccessful dose increase.

- When calculating dose compliance, a "partial" dose will be calculated as 50% of the planned dose amount.

- The initial escalation kit used for Visit 01 is not tracked as part of drug accountability in TEMPO.

- Average daily dose will not be listed by time period.