Boiled Peanut Oral Immunotherapy for the Treatment of Peanut Allergic Pediatric Patients

NCT04090203

Statistical Analysis Plan 3/8/2022

Statistical Analysis Plan

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1 SAP Signatures

I give my approval for the attached SAP entitled BPOIT dated March 8, 2022

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2 Table of Contents

3 Abbreviations and Definitions

ASV	Additional Study Visit
AE	Adverse Event
CoFAR	Consortium of Food Allergy Research
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double Blind Placebo Controlled Food Challenge
EPIT	Epicutaneous Immunotherapy
FAQL	Food Allergy Quality of Life
FAQLQ	Food Allergy Quality of Life Questionnaire
FAQLQ-PF	Food Allergy Quality of Life Questionnaire – Parent Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire – Teenager Form
FPIES	Food Protein-Induced Enterocolitis
ICS	Inhaled Corticosteroid
ITT	Intention To Treat
MID	Minimally Important Difference
OFC	Oral Food Challenge
OIT	Oral Immunotherapy
PA	Peanut Allergy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLIT	Sublingual Immunotherapy
SPT	Skin Prick Test
SV	Study Visit

4 Introduction

4.1 Preface

Peanut allergy (PA) is a common and potentially life threatening condition for which the only current approved management involves strict dietary avoidance. Oral immunotherapy (OIT) is a promising investigational treatment option for this condition, but the widespread clinical use of OIT has been limited by factors including the high rate of adverse events (AEs), including anaphylaxis. Published studies demonstrating the efficacy of OIT in children with peanut allergy, many of which reported high rates of dropout and AEs, have all used peanut products produced by roasting methods, while published data have demonstrated that boiling peanut results in reduced allergenicity without reduction to immunogenicity. In this pilot study, we plan to compare the use of boiled peanut OIT to published data on roasted peanut OIT in children with peanut allergy and hypothesize that the subjects treated with a novel regimen of boiled peanut will demonstrate lower rates of adverse events while demonstrating similar immunologic markers of peanut desensitization and tolerance.

4.2 Scope of the analyses

These analyses will assess the efficacy, safety, and tolerability of boiled peanut immunotherapy on the immune response to peanut protein, with comparison to published data on subjects treated with OIT utilizing a traditional roasted peanut product and will be included in the study report.

5 Study Objectives and Endpoints

5.1 Study Objectives

Primary objective. Determine the effect of boiled peanut immunotherapy on the immune response to peanut and demonstrate that the proportion of subjects successfully desensitized with boiled peanut OIT is not appreciably lower than the proportion of subjects successfully desensitized with roasted peanut OIT in published data.

Secondary objective. Compare the rate of adverse effects of boiled peanut oral immunotherapy to published data on roasted peanut oral immunotherapy.

5.2 Endpoints

Primary Endpoints. Response to treatment defined as ability to successfully consume a single dose of 300 mg or greater of peanut protein with no dose limiting symptoms at exit double blind placebo controlled food challenge (DBPCFC).

The highest dose of roasted peanut protein tolerated by the subject at exit DBPCFC will also be compared to the highest dose tolerated at baseline.

The effect of boiled peanut immunotherapy on the immune response to peanut will be evaluated via specific serum markers of sensitization and tolerance to peanut.

- Levels of serum specific peanut IgE, with higher levels associated with greater likelihood of clinical reaction on exposure to peanut protein.

- Peanut protein component panel, to determine the presence of high levels of sensitivity to peanut proteins known to be associated with severe systemic reactions (Arah 1,2, 3) versus mild reactions (Arah8)
- Levels of peanut specific serum IgG4, with higher levels associated with increased tolerance to peanut protein

These markers will be evaluated at baseline and the conclusion of the study.

Secondary Endpoints. The rate of adverse events in the subjects receiving boiled peanut oral immunotherapy. Possible adverse events include: side effects of treatment defined as oral itching, rhinorrhea, conjunctivitis, urticaria, angioedema, abdominal upset, vomiting, diarrhea, cough, wheeze, or anaphylaxis

- Adverse events will be recorded in terms of the percentage of subjects with adverse events on initial escalation day and at dose escalation visits by CRU staff.
- Adverse events will also be recorded in terms of overall percentage of home doses that result in adverse reaction, with data compiled from home logs.

The adverse reactions will be graded in severity and the treatment required will be recorded.

Validated, age-specific, food-related quality-of-life surveys before and after peanut oral immunotherapy will be completed by all patients/families.

6 Study Methods

6.1 General Study Design and Plan

This study is a prospective single-arm Phase 1 clinical trial providing proof of concept data on boiled peanut oral immunotherapy (OIT) for the treatment of peanut allergy in children. There will be no randomization or blinding.

The primary endpoint of rate of response to treatment will performed as a one-sample superiority test compared to a null hypothesis rate of 20%. Assessments of within-patient changes in maximum tolerated dose, cumulative tolerated dose, immune response, and quality of life will be performed with two-sided tests. Comparisons of adverse event rates will be made to data in published studies of roasted peanut OIT; these comparisons will be descriptive with no hypothesis testing.

For study flow chart, refer to study protocol section 1.2 Study Schema.

6.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion Criteria
Age 1-16 years
History of immediate hypersensitivity reaction to peanut or a high level of suspicion based on testing at the discretion of the investigator
Evidence of IgE mediated peanut hypersensitivity within a 12 month period of study enrollment SPT with wheal/flare of at least 3 x 6 mm and/or Peanut specific IgE >0.35 kU/L

Abbreviations: SPT, skin prick test

In addition, the individual's parent or guardian must provide signed and dated informed consent and the individual must provide signed and dated assent when appropriate. The individual and parent or guardian must agree to comply with all study procedures and the individual must have the ability to take oral medication.

Exclusion Criteria
History of life threatening peanut anaphylaxis
Asthma requiring more than medium dose ICS
Prior participation in OIT, SLIT or EPIT
Oat allergy
Cardiovascular Disease
Use of beta-blockers (oral), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers
Use of steroid medications in the following manners: Daily oral steroid dosing for greater than 1 month during the past year OR Burst or steroid course in the past 3 month before inclusion OR Greater than 2 bursts oral steroid courses in the past year of at least 1 week duration
Pregnancy or lactation
Eosinophilic Gastrointestinal Disease
History of food protein-induced enterocolitis (FPIES)
History of developmental delay or speech delay that precludes age-appropriate communication, in the opinion of the investigator

Abbreviations: ICS, inhaled corticosteroid, OIT, oral immunotherapy, SLIT, sublingual immunotherapy, EPIT, epicutaneous immunotherapy

A history of life-threatening anaphylaxis is defined as a reaction involving respiratory failure, hypotension or neurologic compromise. Medium dose ICS is defined by the National Heart, Lung, and Blood Institute asthma guidelines. Patients with oat allergy, while rare, are to be excluded as this will serve as the placebo for our exit food challenge.

6.3 Study Assessments

The study Schedule of Activities as provided in section 1.3 of the protocol is as follows.

Visit		Study Visit 1	Study Visit 2 Visit 1 +1-4 weeks	SV 3 Visit 2 +2 weeks	SV 4 Visit 2 +4 weeks	SV 5 Visit 2 +6 weeks	SV 6 Visit 2 +8 weeks	SV 7 Visit 2 +10 weeks	SV 8 Visit 2 +12 weeks	SV 9 Visit 2 +14 weeks	SV 10 Visit 1 +18 weeks

Procedures	Enrollment/Baseline visit	Oral Food Challenge	Initial dose escalation	Dose escalation visit 1	Dose Escalation Visit 2	Dose escalation visit 3	Dose escalation visit 4	Dose escalation visit 5	Dose escalation visit 6	Dose escalation visit 7	Oral Food Challenge
Informed Consent	**X**										
Demographics	**X**										
Vitals	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Spirometry*	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood Draw			**X**								**X**
Skin prick test			**X**								**X**
Oral food challenge		**X**									**X**
Urine Pregnancy	**X**										**X**
Study Drug Administration			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Study Drug Compliance				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
AE Review			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Conmed Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
FAQL Questionnaire	**X**										**X**

Due to the difficulties of scheduling study visits during the COVID-19 pandemic, the primary analysis will not place any limitations on the timing of study visits. All study visits will be analyzed in order by date, and the number of days from initial oral food challenge (OFC) and initial dose escalation visit will be reported for each study visit. If more than seven dose escalation visits are required as described in the study protocol section 6.1.1 'Study Intervention Description', the additional study visits will be named 'Additional Study Visit 9.1' through 'Additional Study Visit 9.*x*' for the purposes of analysis and reporting.

6.3.1 Assessment of Primary Efficacy Endpoint

The primary efficacy endpoint is 'response to treatment' defined as ability to successfully consume a single dose of 300 mg or greater of peanut protein with no dose limiting symptoms at the exit DBPCFC. This endpoint will be analyzed as a binary variable (yes response to treatment/no response to treatment).

6.3.2 Assessment of Secondary Efficacy Endpoints

Highest tolerated dose and cumulative dose. The highest dose of roasted peanut protein tolerated by the subject, cumulative total dose of roasted peanut protein tolerated by the subject, and the changes in highest tolerated dose and cumulative tolerated dose from initial OFC to the peanut protein arm of the exit DBPCFC will be analyzed as ordinal variables because of the interval nature of the dosing schedule (Chinchilli et al., 2005). The dose schedule for initial OFC and exit DBPCFC is shown below.

Peanut protein challenge dose schedule at initial (SV 1) and exit (SV 10) oral food challenges.

Oral food challenge	Highest tolerated dose of peanut protein (mg)	Cumulative tolerated dose of peanut protein (mg) at initial OFC	Cumulative tolerated dose of peanut protein (mg) at exit DBPCFC
Initial only	5	5	
Initial only	10	15	
Initial and Exit	25	40	25
Initial only	50	90	
Initial and Exit	100	190	125
Exit only	200		325
Exit only	300		625
Initial only	500	690	
Exit only	600		1225
Initial and Exit	1000	1690	2225
Initial only	4000	5690	

Serum markers of sensitization and tolerance to peanut. Changes in serum markers of sensitization and tolerance to peanut from initial dose escalation visit to final study visit will be analyzed as continuous variables.

Food Allergy Quality of Life Questionnaires (FAQLQ). The Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) will be used for patients aged 0-12 years (DunnGalvin et al., 2008). The Food Allergy Quality of Life Questionnaire –Teenager Form (FAQLQ-TF) will be used for patients aged 13-17 year (Flokstra-de Blok et al., 2008). For all FAQLQ surveys, all questions are scored on an ordered scale from 1 (“no impairment”) to 7 (“maximal impairment”) for calculations. Subscale and summary scores are calculated as item mean scores, on the same scale from 1 to 7. Subscale and summary scores, and changes in subscale and summary scores from enrollment/baseline visit to final study visit, will be analyzed as continuous variables. The MID (minimally important difference) for the FAQLQ is 0.5 (DunnGalvin et al., 2010), and the change in total score will be dichotomized as greater than or equal to 0.5 or less than 0.5 and analyzed as a binary variable. Scoring of the FAQLQ is detailed in section 9.3.2.

6.3.3 Assessment of Safety Endpoints

AEs, including Serious Adverse Events (SAEs) will be graded according to severity using the Consortium of Food Allergy Research (CoFAR) scale, which is 5-point ordered scale from mild (1) to death (5). AEs will be categorized by preferred term using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and for the specific AEs for interest listed in section 5.2, by treatment required, and by study phase (dose escalation study visits, home doses, exit DBPCFC, and overall).

7 Sample Size

We will compare with proportion of patients successfully desensitized as defined by meeting the primary endpoint with the expected placebo rate. The null hypothesis is that the proportion of patients successfully desensitized by boiled peanut oral immunotherapy will not be greater than the expected 20% that has been previously published as the proportion of patients successfully meeting the primary endpoint in OIT studies (which aligns with the expected 20% that would naturally "outgrow" a peanut allergy). If we reject this null hypothesis, we will be able to conclude that the proportion of successfully desensitized by boiled peanut therapy is greater than placebo. The sample of 10 patients will provide >90% power to determine the expected success rate (80%) is greater than a theoretical placebo rate (20%).

8 General Analysis Considerations

8.1 Timing of Analyses

No interim analyses are planned. The final analysis will be performed on data transferred to the study statistician, having been documented as meeting the cleaning and approval requirements of the study protocol and after the finalization and approval of this SAP document.

8.2 Analysis Populations

8.2.1 Primary Endpoint Intention to Treat (ITT) Population

- *All patients enrolled in study following the initial OFC.*

8.2.2 Efficacy Population

- *All patients who completed both initial OFC and exit DBPCFC.*

8.2.2.1 Modified Efficacy Population for Immune Response

- *Patients with serum testing for at least one peanut-specific marker of sensitization and tolerance at both the initial dose escalation visit and exit DBPCFC.*

8.2.2.2 Modified Efficacy Population for FAQLQ-PF

- *Patients with at least one subscale or summary score at both enrollment/baseline and exit DBPCFC, on the same FAQLQ age-group-specific parent form.*

8.2.2.3 Modified Efficacy Population for FAQLQ-TF

- *Patients with at least one subscale or summary score on the FAQLQ teenager form at both enrollment/baseline and exit DBPCFC.*

8.2.3 Safety Population

- *All enrolled patients who took at least one dose of study medication during any dose escalation visit or at home, or participated in either arm of the exit DBPCFC.*

8.2.4 Study Visit Populations

- *For each SV, all patients with a documented date of visit.*

8.3 Covariates and Subgroups

No subgroup analyses are planned.

8.4 Missing Data

With the exception of the primary endpoint, missing data will not be imputed and analyses will be performed on a complete-case basis, due to the small sample size and exploratory nature of the study. The expected sample size is smaller than is practical to analyze under multiple imputation, with little ability to assess the missing at random assumption. A carry-forward approach is likely to be too conservative to provide useful information for future study planning or hypothesis generation. Patients with missing data on particular endpoints will be excluded only for analyses in which those variables were used, and the results of the complete-case analyses will be interpreted as pertaining to patients with data on the specific analyzed endpoint. Sample sizes will be noted for all descriptive statistics and analyses.

8.5 Multiple Testing

As this is a proof-of-concept study with a single primary endpoint, no adjustment for multiple testing will be performed. The use of hypothesis testing is limited to primary and secondary efficacy endpoints, and within the FAQLQ analysis, to total scores only. Detailed descriptive statistics will be presented for secondary endpoints, along with unadjusted p-values, and reports will interpret hypothesis testing for secondary endpoints as hypothesis-generating rather than confirmatory.

9 Summary of Study Data

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), median, 25^{th} and 75^{th} percentiles, maximum, and minimum (range). Categorical variables will be summarized with the frequency and percentages (calculated using the non-missing sample size as the denominator) of observed levels. All summary tables will list the total analysis population and missing data for the table, and for individual variables in the table where different from the total. Data listings will be sorted by subject and, where necessary, by visit number within subject.

Because the secondary efficacy analyses of changes in highest tolerated dose and cumulative dose of peanut protein, serum markers of sensitization and tolerance to peanut, and FAQLQ scores will be performed on a complete-case basis, the sample sizes of non-missing data for the initial and final values may be larger than the sample sizes of non-missing data for the change variables. Therefore additional descriptive tables will present univariable summary statistics for all non-missing data for the initial and final values of these variables. (Refer to mock Tables 4.3-4.6.)

9.1 Subject Disposition

All subjects in the study database will be considered as assessed for eligibility. Subject disposition will be described based on the database fields on the case report forms (CRFs) 'Inclusion/Exclusion BPOIT', 'Demographics' (field indicating date of signed consent), 'Oral Food Challenge' (field indicating date of participation), 'Study drug administration' (any dose of study medication administered indicates enrollment in study), 'Off study/continued therapy' (field indicating the reason the patient came off the study). (Refer to mock Table 1.1.)

9.2 Derived variables

9.2.1 Derivation of Primary Efficacy Endpoint

The primary efficacy endpoint is 'response to treatment' at the exit DBPCFC. A subject will be defined to have response to treatment if the question, 'Was 300mg dose tolerated' on the CRF corresponding to the peanut protein arm of the DBPCFC was marked 'Yes'. If this question is marked 'No', or the subject did not complete the DBFCFC for any reason, the subject will be defined as no response to treatment.

9.2.2 Derivation of Secondary Efficacy Endpoints

Highest tolerated dose and cumulative dose. The highest tolerated dose at initial OFC will be the largest amount in milligrams to which the question, 'Was *amount* dose tolerated' on the CRF for the initial OFC was marked 'Yes'. The highest tolerated dose at exit DBFCFC will be the largest amount in milligrams to which the question, 'Was *amount* dose tolerated' was marked 'Yes' on the CRF corresponding to the peanut protein arm of the exit DBPCFC. At both the initial OFC and exit DBPCFC, if the lowest dose given was not tolerated, the highest tolerated dose will be zero. The change in highest tolerated dose will be calculated as the difference between the final and initial highest tolerated doses.

The cumulative tolerated dose at initial OFC will be the sum in milligrams of all doses in which the question, 'Was *amount* dose tolerated' on the CRF for the initial OFC was marked 'Yes'. The cumulative tolerated dose at exit DBPCFC will be the sum in milligrams of all doses in which the question, 'Was *amount* dose tolerated' was marked 'Yes' on the CRF corresponding to the peanut protein arm of the DBPCFC. At both the initial OFC and exit DBFCFC, if the lowest dose given was not tolerated, the cumulative tolerated dose will be zero. The change in cumulative tolerated dose will be calculated as the difference between the final and initial highest tolerated doses.

Serum markers of sensitization and tolerance to peanut. The change in each serum marker will be calculated as the difference between the final and initial values.

FAQLQ. Questionnaires will be scored according to scoring sheets downloaded from the FAQLQ website (faqlq.com, accessed November 1, 2021). The change in the summary score and each subscale score from baseline to follow-up FAQLQ will be calculated for each patient. The MID (minimally important difference) for the FAQLQ is 0.5 (DunnGalvin et al., 2010); each change score will be categorized as greater than or equal to the MID (>= 0.5), or less than the MID (< 0.5). The number and percent of missing items will be assessed for the summary score and each subscale score, and scores will not be calculated if the percent of missing items is greater than 20%, as recommended on the FAQLQ website (http://faqlq.com/?page_id=15). *Item mean score*s will be calculated as the sum of all non-missing item response values divided by the number of non-missing items.

- Subjects ages 0-12 years. The Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) for ages 0-12 years has different scoring sheets for age group 0-3, 4-6, and 7-12; there are 3 subscale scores and a summary score for all age groups (http://faqlq.com/wp-content/uploads/2011/11/FAQLQ-PF-scoring-sheet-all-age-groups.pdf). Subscale scores are item mean scores for the specified questions, and the summary score is the mean of the three subscale scores. If one or more subscale scores cannot be calculated due to missing data, the summary score will not be calculated. Figures 9.1-9.3 show the scoring sheets.

- Subjects ages 13-17 years. The Food Allergy Quality of Life Questionnaire –Teenager Form (FAQLQ-TF) for ages 13-17 years has 3 subscale scores and a summary score (http://faqlq.com/wp-content/uploads/2011/11/FAQLQ-TF-scoring-sheet.pdf). Subscale scores are item mean scores for completed items, and the summary score is the item mean score of all questionnaire items for completed items. If one or more subscale scores cannot be calculated due to missing data but the overall survey completeness is not lower than 80%, the summary score will be calculated. Figure 9.4 shows the scoring sheet.

Figure 9.1. FAQOL-PF scoring sheet for ages 0-3 years.

FAQoL-PF SCORING SHEET (0-3yrs)

1. Emotional Impact (EI) Subscale		2. Food Anxiety (FA) Subscale		3. Social and Dietary Limitations (SDL) Subscale	
Question	**Score (0-6)**	**Question**	**Score (0-6)**	**Question**	**Score (0-6)**
Input score for each question below		Input score for each question below		Input score for each question below	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9				**Q. 13**	
Q. 10				**Q. 14**	
Q. 11					
Total		**Total**		**Total**	
Total / 6 = EI Subscale Score		Total / 3 = FA Subscale Score		Total / 5 = SDL Subscale Score	
EI Subscale Score =		**FA Subscale Score =**		**SDL Subscale Score =**	

HRQoL Summary Score = (EI Subscale Score + FA Subscale Score + SDL Subscale Score) / 3

HRQoL Summary Score = (_____ + _____ + _____) / 3 = _____

Figure 9.2. FAQOL-PF scoring sheet for ages 4-6 years.

FAQoL-PF SCORING SHEET (4-6yrs)

1. Emotional Impact (EI) Subscale		2. Food Anxiety (FA) Subscale		3. Social and Dietary Limitations (SDL) Subscale	
Question	**Score (0-6)**	**Question**	**Score (0-6)**	**Question**	**Score (0-6)**
Input score for each question below		Input score for each question below		Input score for each question below	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9		**Q. 16**		**Q. 13**	
Q. 10		**Q. 17**		**Q. 14**	
Q. 11		**Q. 20**		**Q. 15**	
Q. 23		**Q. 21**		**Q. 18**	
Q. 24				**Q. 19**	
Q. 25				**Q. 22**	
Q. 26					
Total		**Total**		**Total**	
Total / 10 = EI Subscale Score		Total / 7 = FA Subscale Score		Total / 9 = SDL Subscale Score	
EI Subscale Score =		**FA Subscale Score =**		**SDL Subscale Score =**	

HRQoL Summary Score = (EI Subscale Score + FA Subscale Score + SDL Subscale Score) / 3

HRQoL Summary Score = (_____ + _____ + _____) / 3 = _____

Figure 9.3. FAQOL-PF scoring sheet for ages 7-12 years.

FAQoL-PF SCORING SHEET (7-12yrs)

1. Emotional Impact (EI) Subscale		2. Food Anxiety (FA) Subscale		3. Social and Dietary Limitations (SDL) Subscale	
Question	**Score (0-6)**	**Question**	**Score (0-6)**	**Question**	**Score (0-6)**
Input score for each question below		Input score for each question below		Input score for each question below	
Q. 2		**Q. 1**		**Q. 3**	
Q. 6		**Q. 4**		**Q. 8**	
Q. 7		**Q. 5**		**Q. 12**	
Q. 9		**Q. 16**		**Q. 13**	
Q. 10		**Q. 17**		**Q. 14**	
Q. 11		**Q. 20**		**Q. 15**	
Q. 23		**Q. 21**		**Q. 18**	
Q. 24		**Q. 29**		**Q. 19**	
Q. 25				**Q. 22**	
Q. 26					
Q. 27					
Q. 28					
Q. 30					
Total		**Total**		**Total**	
Total / 13 = EI Subscale Score		Total / 8 = FA Subscale Score		Total / 9 = SDL Subscale Score	
EI Subscale Score =		**FA Subscale Score =**		**SDL Subscale Score =**	

HRQoL Summary Score = (EI Subscale Score + FA Subscale Score + SDL Subscale Score) / 3

HRQoL Summary Score = (_____ + _____ + _____) / 3 = _____

Figure 9.4. FAQOL-TF scoring sheet.

FAQLQ-TF SCORING SHEET (13-17 years)

Allergen avoidance & dietary restrictions (AADR)		Risk of accidental exposure (RAE)		Emotional impact (EI)	
Question	**Score** (range 1-7)	**Question**	**Score** (range 1-7)	**Question**	**Score** (range 1-7)
Add up the score of each question		Add up the score of each question		Add up the score of each question	
Q. 1		**Q. 11**		**Q. 5**	
Q. 2		**Q. 13**		**Q. 12**	
Q. 3		**Q. 14**		**Q. 19**	
Q. 4		**Q. 15**		**Q. 20**	
Q. 6		**Q. 17**		**Q. 21**	
Q.7		**Q. 18**		**Q. 22**	
Q. 8				**Q. 23**	
Q. 9					
Q. 10					
Q. 16					
	_____ +		_____ +		_____ +
Total		**Total**		**Total**	
Total / number of completed questions=AADR domain score		Total / number of completed questions = RAE domain score		Total / number of completed questions = EI domain score	
AADR Domain Score = (_____) / (_____) = _____		**RAE Domain Score =** (_____) / (_____) = _____		**EI Domain Score =** (_____) / (_____) = _____	

Total FAQLQ-TF Score = (q1 + q2 + q3 + q4 + q5 + q6 + q7 + q8 + q9 + q10 + q11 + q12 + q13 + q14 + q15 + q16 + q17 + q18 + q19 + q20 + q21 + q22 + q23) / number of completed questions

Total FAQLQ-TF Score = (_____) / (_____) = _____

9.2.3 Derivation of Safety Variables

Adverse events (AEs) will be categorized by preferred term using the CTCAE Version 5.0, and by the specific AEs of interest listed in section 5.2. The *specific AEs of interest* with possible alternative preferred terms, which will be grouped together, are: oral itching (oral pruritus), rhinorrhea (allergic rhinitis or rhinorrhea), conjunctivitis (eye itching), urticaria (hives), angioedema, abdominal upset (dyspepsia or nausea), vomiting, diarrhea, cough, wheeze (wheezing), and anaphylaxis.

Mortality. Mortality will be identified by an AE of CoFAR severity grade 5, and/or 'Death' indicated as a SAE criteria on the CRF for AEs.

9.2.4 Derivation of Other Variables

Age at initial OFC. Age will be calculated using the date of birth (DOB) and the date of the OFC, and presented as age at last birthday as an integer.

Timing of Study Visits (SVs) and Additional Study Visits (ASVs). The number of days from initial OFC and initial dose escalation visit will be calculated for each SV or ASV as the difference in the two dates (Date of SV/ASV – Date of OFC/initial dose escalation visit). (Refer to mock Table 1.4)

9.3 Demographic and Baseline Variables

Demographic data presented will be age at OFC, gender, ethnicity, and race. Baseline/enrollment variables presented will be height, weight, and known history of asthma, allergic rhinitis, and atopic dermatitis. Demographic data will be summarized in separate columns for the Intention to Treat, Efficacy, and Safety populations; if any of these represent the same population, the columns will be combined. (Refer to mock Table 1.3.)

9.4 Study Drug Administration

For each patient and each dose escalation visit, the maximum dose tolerated (mg) and dose to be taken at home (mg), as reported on the CRF for study drug administration, will be listed for the ITT population (all enrolled patients) in a single table. (Refer to mock Table 4.1.)

9.5 Treatment Compliance

Treatment compliance will be summarized separately for each SV and ASV using fields from the CRF for study drug compliance, including the number of patients with at least one missed dose and reasons for missed doses reported by at least one patient. The population for each SV table will be all patients in the corresponding Study Visit population. (Refer to mock Tables 4.2.1 -4.2.10.)

10 Efficacy Analyses

10.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is 'response to treatment' defined as defined as ability to successfully consume a single dose of 300 mg or greater of peanut protein with no dose limiting symptoms at the exit DBPCFC. The analysis population will be the Primary Endpoint ITT population. Subjects with missing data on the primary endpoint will be considered as non-responders for the primary analysis. Due to the small sample size, exact rather than asymptotic statistical methods will be used for the analysis of this endpoint.

The proportion of patients who respond to treatment will be assessed using a one-sample superiority analysis compared to an expected proportion of 20%. The null hypothesis is that the proportion of patients who respond to treatment is less than or equal to 20%, and the alternative hypothesis is that the proportion of patients who respond to treatment is greater than 20%.
As this is a proof-of-concept study, statistical significance in the analysis of primary efficacy endpoint will be assessed using a one-sided 0.05 level of significance (or two-sided 0.1) rather than a one-sided 0.025 level of significance (or two-sided 0.05). The alternative hypothesis of superiority will be accepted if the lower bound of the one-sided 95% Clopper-Pearson exact confidence interval (equivalent to the lower bound of a two-sided 90% confidence interval) for the primary efficacy endpoint is greater than 20%; the p-value for the exact binomial test at a one-sided significance level of 0.05 will also be provided. The summary statistics will be reported as described in section 9. (Refer to mock Table 2.1.)

10.2 Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints consist of changes in continuous or ordinal variables from the

enrollment/baseline, initial OFC, or initial dose escalation visit to the final study visit. The primary analyses of the change endpoints will be performed using Wilcoxon signed rank tests, with null hypotheses of no change, versus two-sided alternative hypotheses at a significance criteria of 0.05. Missing data will not be imputed, and complete cases only will be analyzed (see section 8.4). Due to the small sample size, visual assessments of the symmetry assumptions of the Wilcoxon signed rank tests are unlikely to be definitive, and p-values for Sign tests under the same null hypotheses and significance criteria will also be presented as sensitivity analyses. The summary statistics will be reported as described in section 9.

Highest tolerated dose and cumulative tolerated dose. Changes in highest tolerated dose and cumulative tolerated dose from initial OFC to the peanut protein arm of the exit DBPCFC will be analyzed as ordinal variables, using nonparametric tests. The analysis population will be the Efficacy Population. (Refer to mock Table 2.3.)

Serum markers of sensitization and tolerance to peanut. Changes in serum markers of sensitization and tolerance to peanut will be analyzed as continuous variables using nonparametric tests. The analysis population will be the Modified Efficacy Population for immune response. (Refer to mock Table 2.4.)

FAQLQ. Changes in FAQLQ subscale and summary scores will be analyzed as continuous variables using nonparametric tests. The percent of patients with change in summary score greater than or equal to the MID will be reported with 95% Clopper-Pearson exact confidence interval. Hypothesis testing will be performed for summary scores only. Parent and Teenager forms will be analyzed separately, and the analysis populations will be the Modified Efficacy Populations for FAQLQ-PF and FAQLQ-TF. (Refer to mock Tables 2.5 and 2.6.)

11 Safety Analyses

Safety analyses will be performed on the safety population unless otherwise specified. Summary statistics will be reported as described in section 9.

11.1 Adverse Events

All AEs that affect at least one patient will be reported. AEs will be *categorized* as corresponding to a study phase (dose escalation study visit, home dose, exit DBPCFC, etc.), and reported within study phase and overall. They will be further *grouped* by preferred term, CoFAR severity grade, or treatment given. AEs that meet SAE criteria will also be categorized as corresponding to a study phase, and reported within study phase and overall. Adverse events data will be tabulated within the categories and groups described above at both the *patient* and *dose* level.

Patient-level analysis. The *number of patients* that experience the AE or SAE at least once will be tabulated. Within category and group, each subject will be counted once and any repetitions will be ignored.

Dose level analysis. The *number and percentage of study medication doses* in the category and group that are associated with the AE or SAE. The total number of doses of study medication will be reported for each category, and the denominator for the calculation of the percentages will be the total number of doses given by category.

11.1.1 Patient- and dose-level summary AE tables

AEs will be classified into study phases as follows: dose escalation study visits, home doses, exit

DBPCFC, and overall. Specific AEs of interest, which will be included in the patient- and dose-level AE tables whether or not any patients experienced them, are listed under Secondary Endpoints in section 5.2 and under Derivation of Safety Variables in section 9.2.3. Any additional preferred terms recorded for at least one patient or dose will also be reported, listed alphabetically following the specific AEs of interest. AEs occurring and doses of study medication administered during both arms of the exit DBPBFC will be counted towards the totals. (Refer to mock Tables 3.1 and 3.2.)

11.1.2 Comparative AE table

AE data from this study will be compared descriptively to the AE data from three published studies: the study medication arms of the Phase 2 and Phase 3 trials of AR101 OIT for peanut allergy (Bird et al., 2018; Vickery et al. for PALISADE, 2018), and OIT data from the PACE meta-analysis study of OIT for peanut allergy (Chu et al., 2019). No hypothesis testing will be performed.

For this table, study AEs will be categorized into two study phases as best corresponds to the comparative data: 1) initial dose escalation study visit, and 2) an increasing dose phase which includes all other dose escalation study visits and home doses, but excludes the exit DBPCFC. AEs will be grouped into severity grades, treatments, and preferred terms, where the preferred term list will include the specific AEs of interest only (see sections 5.2 and 9.2.3). (Refer to mock Table 3.3 for comparative data and source information.)

11.1.3 ClinicalTrials.gov 'Other (Not Including Serious) Adverse Events' table

The adverse event term list will include all preferred terms recorded for at least one patient, listed alphabetically. AEs which meet SAE Criteria will be excluded from the calculations for this table. (Refer to mock Table 3.4.)

11.2 Deaths, Serious Adverse Events and other Significant Adverse Events

11.2.1 Patient- and dose-level summary AE tables

SAEs will be included in the patient- and dose-level summary AE tables described in section 11.1.1 as a subset of the AEs.

11.2.2 ClinicalTrials.gov 'Serious Adverse Events' table

The adverse event term list will include all preferred terms recorded for at least one patient and meeting SAE criteria, listed alphabetically. (Refer to mock Table 3.5.)

11.2.3 ClinicalTrials.gov mortality table

The total number of patients and the number of patients who died due to AEs will be presented. (Refer to mock Table 3.6.)

11.3 Concomitant Medications

Current medications (listed alphabetically) will be summarized by medication name (as recorded on the concomitant medication CRF), the number of patients who reported using each medication at least once, and the total number of occurrences of use of the medication. The ITT population (all enrolled patients) will used for this analysis. (Refer to mock Table 3.7.)

11.4 Other Safety Measures

Vital signs. For each patient, general appearance and vital signs will be listed at each study visit. The ITT population (all enrolled patients) will used for this analysis. (Refer to mock Table 3.8.)

Accidental peanut consumption. All reported incidents of accidental peanut consumption will be

listed, sorted by patient number and time from initial dose escalation visit. Patients with no accidental peanut consumption will not be listed in the table. The ITT population (all enrolled patients) will used for this analysis. (Refer to mock Table 3.9.)

Spirometry. Spirometry was performed at the physician's discretion per protocol. When performed, spirometry results at enrollment/baseline, exit DBPCFC, and any other visits will be listed for each patient in a single table. The ITT population (all enrolled patients) will used for this analysis. (Refer to mock Table 3.10.)

Peak flow. Peak flow was performed at the physician's discretion per protocol. When performed, peak flow results at each visit will be listed for each patient in a single table. The ITT population (all enrolled patients) will used for this analysis. (Refer to mock Table 3.11.)

12 Reporting Conventions

P-values greater than 0.01 will be reported to 2 decimal places, p-value between 0.01 and 0.001 inclusive will be reported to 3 decimal places, and p-values less than 0.001 will be reported as "<0.001". Quantiles, such as median, quartiles, minimum, and maximum will use the same number of decimal places as the original data. Percentages will be reported to one-tenth of a percent, with values less than one-tenth of a percent reported as "<0.1" and zero percent reported as 0. FAQLQ subscale and summary scores will be reported to one decimal place. All other statistics will be reported to one decimal place greater than the original data.

13 Quality Assurance of Statistical Programming

All data, code, and study information will be stored on Cleveland Clinic Lerner Research Institute's password protected servers. Each biostatistician's final code, log files, output, and derived datasets will be saved separately within a shared project directory. At the time of writing, all analyses will be performed on SAS 9.4 software via SAS Studio (SAS Institute, Cary, NC) installed on a Linux platform on the Lerner Research Institute's servers. Sarah Worley, MS and Wei Liu, MS, or similarly-qualified biostatisticians in the Department of Quantitative Health Sciences at Cleveland Clinic, will independently produce the tables listed in the Statistical Analysis Plan and compare the results, and the trial statistician will review code and output as necessary.

14 Listing of Tables

Background and demographic data
Table 1.1 Disposition of patients.
Table 1.2 Analysis populations.
Table 1.3 Demographics and baseline characteristics.
Table 1.4 Timing of study visits (ITT population).

Efficacy endpoints
Table 2.1 Primary endpoint: Response to treatment (ITT population).
Table 2.2 Listing of oral food challenge results by patient (ITT population).
Table 2.3 Summary of changes in maximum tolerated dose and cumulative tolerated dose, from initial OFC to exit DBPCFC (Efficacy population, N=X).
Table 2.4 Summary of changes in serum markers of sensitization and tolerance to peanut (Modified Efficacy population for immune response, N=X).
Table 2.5 Summary of changes in parent-reported Food Allergy Quality of Life (FAQLQ-PF) scores (Modified Efficacy Population for FAQLQ-PF).
Table 2.6 Summary of changes in child-reported Food Allergy Quality of Life (FAQLQ-TF) scores (Modified Efficacy Population for FAQLQ-TF).

Safety endpoints
Table 3.1 Patient-level summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) (Safety Population).
Table 3.2 Dose-level summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) (Safety Population).
Table 3.3 Comparison of Adverse Events (AEs) and Serious Adverse Events (SAEs) to published data (Safety Population).
Table 3.4 ClinicalTrials.gov reporting requirement 'Other (Not Including Serious) Adverse Events' (Safety Population).
Table 3.5 ClinicalTrials.gov reporting requirement 'Serious Adverse Events' (Safety Population).
Table 3.6 ClinicalTrials.gov reporting requirement for mortality (ITT population).
Table 3.7 Summary of concomitant medications (ITT population).
Table 3.8 Listing of general appearance and vital signs by patient-visit (ITT population).
Table 3.9 Listing of episodes of accidental peanut consumption (ITT population).
Table 3.10 Listing of spirometry results by patient-visit (ITT population).
Table 3.11 Listing of peak flow results by patient-visit (ITT population).

Additional study data
Table 4.1 Listing of study drug administration by patient-visit (ITT population).
Tables 4.2.*x* Summary of study drug compliance for Study Visit *x* (Study visit populations).
Table 4.3 Summary of maximum and cumulative maximum tolerated doses, at initial OFC and exit DBPCFC (Study visit populations).
Table 4.4 Summary of allergen, peanut IgE and skin prick test data, at initial OFC and exit DBPCFC (Study visit populations).
Table 4.5 Summary of FAQLQ-PF summary and subscale scores, at enrollment/baseline and follow-up visit (Study visit populations).
Table 4.6 Summary of FAQLQ-TF summary and subscale, at enrollment/baseline and follow-up visit (Study visit populations).

15 References

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16 Appendices

Appendix I: Mock Tables.