DAIT/RHO STATISTICAL ANALYSIS PLAN
26 OCT 2022

CONSORTIUM FOR FOOD ALLERGY RESEARCH

PROTOCOL CoFAR-11
(Stage 1 and Stage 1 Open Label Extension)

Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults

OUtMATCH

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Document History

Version	Date	Significant Changes from Previous Version
1.0	11 JUN 2019	V1.0
2.0	26 OCT 2022	• Removed peak flow from demographics summary • Added Asthma Control Questionnaire to demographics summary • Added separate supportive analysis of the primary endpoint that excludes participants who had dose-limiting symptoms to the 300 mg dose of placebo used in the blinded OFC to peanut during the Screening DBPCFC • Modified analyses to address participants that restarted a stage • Added summaries describing issues related to COVID-19 • Removed order of blinded OFC to peanut during DBPCFC at the end of Stage 1 for endpoints not defined by the results of the DBPCFC • Changed times of complete physical examinations to correspond with Protocol Version 2.0 and later • Modified classifications of treatment-emergent adverse events • Defined how medications will be classified into stages • Added analysis populations to be used for summarizing reactions to DBPCFCs • Added summaries for protocol deviations during screening • Added AE summaries for study procedures • Added summaries describing dose-limiting symptoms during DBPCFCs, events of anaphylaxis, and epinephrine use. • Added the estimands framework for primary and key secondary endpoints.

		• Added planned Interim Analysis • Updated approach for Type I error control • Changed analysis of primary and key secondary endpoints to be based on Fisher's exact test rather than logistic regression. The latter is included as supportive analyses. • Clarified use of exact logistic regression and remove reference to Wald for efficacy assessment • Relabeled analysis populations for clarity • Clarified language and intentions throughout with respect to planned analyses and data displays • Added forest plots for AEs • Clarified continuous variables will be summarized with n, mean, SD, median, min, max unless stated otherwise • Updated convention for reporting p-values to use 5 decimal places

Table of Contents

GLOSSARY OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BLS1	baseline for Stage 1
CBC	complete blood count
CoFAR	Consortium for Food Allergy Research
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
DAIT	Division of Allergy, Immunology, and Transplantation
DBPCFC	double-blind placebo-controlled food challenge
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EoE	eosinophilic esophagitis
FAQLQ	Food Allergy Quality of Life Questionnaire
FAQLQ-AF	Food Allergy Quality of Life Questionnaire – Adult Form
FAQLQ-PF	Food Allergy Quality of Life Questionnaire – Parent Form
FAQLQ-CF	Food Allergy Quality of Life Questionnaire – Child Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire – Teenager Form
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FA-S1	full analysis set – Stage 1
FA-S1OLE	full analysis set – Stage 1 OLE
FVC	forced vital capacity
GI	gastrointestinal
GINA	Global Initiative for Asthma
HLGT	high level group term
HLT	high level term
ICH	International Conference on Harmonisation
ID	identifier
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4

IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
MAR	missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing-not-at-random
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OFC	oral food challenge
OIT	oral immunotherapy
OLE	open label extension
PD	pharmacodynamic
PEF	peak expiratory flow
PFA-S1	pediatric full analysis set – Stage 1
PFA-S1OLE	pediatric full analysis set – Stage 1 OLE
PI	(CRU) Principal Investigator
PK	pharmacokinetic
PPP-S1	pediatric per-protocol set – Stage 1
PSS-PRERAND-S1	pediatric pre-randomization safety set-Stage 1
PSS-S1OLE	pediatric safety set-Stage 1 OLE
PSS-S1	pediatric safety set-Stage 1
PSS-OFC-S1OLE	pediatric safety set for OFCs- Stage 1 OLE
PSS-PRERAND-OFC-S1	pediatric pre-randomization safety set for screening OFCs-Stage 1
PSS-OFC-S1	pediatric safety set of OFCs- Stage 1
SACCC	Statistical and Clinical Coordinating Center
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SMQ	standardized MedDRA query
SOC	system organ class
SPT	skin prick test
SS-S1	safety set – Stage 1
SS-S1OLE	safety set – Stage 1 OLE
SS-PRERAND-S1	pre-randomization safety set
SS-OFC-S1OLE	safety set for OFCS – Stage1 OLE

SS-PRERAND-OFC-S1	pre-randomization safety set for Screening OFCs
SS-OFC-S1	safety set for OFCs – Stage 1
TEAE	treatment-emergent AE
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

The protocol synopsis is available in the most recent IRB-approved version of the OUtMATCH protocol.

2. INTRODUCTION

This SAP is based on Section 13 (Statistical Considerations and Analysis Plan) of the OUtMATCH protocol. However, the analyses specified in this document supersede the high-level analysis plan described in the protocol. The SAP contains detailed information to aid in the implementation of the statistical analyses and reporting of the study data from Stage 1 and Stage 1 OLE of this study. This SAP was written with consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP briefly summarizes the protocol, defines the Stage 1 and Stage 1 OLE analysis populations, and describes the analyses to support a) the planned interim analysis, b) clinical study report (CSR) submissions, and c) other analyses to be included as part of manuscript development.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)". Percentages will be rounded to one decimal place. If a count is 0, 0% will be shown for the percentage. To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no participants had a response in a particular category.
- Continuous variables will be summarized using n, mean, standard deviation, minimum, maximum, and median, as appropriate. The mean will be reported at one more significant digit than the precision of the data, the standard deviation will be reported at two more significant digits than the precision of the data, and minimum, maximum, and median will be reported at the same precision as the data. The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics, including t, z, and $\chi 2$ test statistics, will be reported to two decimal places.
- P-values < 0.00001 will be displayed as "<0.00001" otherwise, p-values will be displayed to 5 decimal places.
- Unless otherwise stated, all statistical tests will be conducted at the 0.05 2-tailed alpha level.
- All analyses described in the SAP will be performed using SAS® System Version 9.4 or later or R Version 3.5 or later. All analyses that will be included in the CSR will be performed using SAS® System Version 9.4 or later.
- Dates in listings will be displayed as yyyy-mm-dd (e.g., 2005-01-24).
- Age at screening will be calculated in years using the date of birth and the date of Screening as [((intck('month', birthday, screening_date) - (day(screening_date) < day(birthday))) / 12)]. Age at

randomization will be calculated in years using the date of birth and the date of randomization as [((intck('month', birthday, rand_date) - (day(rand_date) < day(birthday))) / 12)]. In the analysis datasets and tables, age will be reported to 1 decimal place. In listings, age will be reported in years.

- Data listings provided for the Stage 1 population will identify participants who are also included in the Stage 1 OLE population. Each listing will be sorted by age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, and participant identifier (ID).

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SETS

Analysis populations for Stage 1 and Stage 1 OLE are described below. In the event this SAP specifies analyses/data summaries to be repeated for multiple populations, but the populations are found to be identical, reductant output will not be produced.

For the interim analysis of efficacy and for the associated study report (if the Stage 1 is curtailed for efficacy), the analysis populations will be subset on all pediatric participants randomized into Stage 1 by 08JUL2022 (N=165) with the addition of one additional supporting analysis that will also include adults.

4.1. Stage 1 Analysis Populations

Pediatric Full Analysis Set - Stage 1 (PFA-S1): All participants aged less than 18 years at randomization who have been randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment actually received in Stage 1.

Full Analysis Set - Stage 1 (FA-S1): All participants who have been randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment actually received in Stage 1.

Pediatric Per-Protocol Set - Stage 1 (PPP-S1): All participants in the PFA-S1 population who have completed at least 75% of scheduled injections with either omalizumab or placebo for omalizumab in Stage 1 and have completed the blinded OFC to peanut during the DBPCFC at the end of Stage 1. The PPP-S1 population will only include participants who receive the correct treatment according to their randomization assignment and correct omalizumab dosing frequency in Stage 1. Participants with major protocol deviations that could be expected to materially affect efficacy during Stage 1 will also be excluded from PPP-S1.

Pediatric Safety Set - Stage 1 (PSS-S1): All randomized participants aged less than 18 years at randomization who have received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as “omalizumab” if a participant received any dose (including a partial single dose) of

omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

Safety Set - Stage 1 (SS-S1): All participants who have received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

Pediatric Pre-Randomization Safety Set - Stage 1 (PSS-PRERAND-S1): All randomized participants aged less than 18 years at randomization and all participants who are enrolled but never randomized aged less than 18 years at screening.

Pre-Randomization Safety Set - Stage 1 (SS-PRERAND-S1): All randomized participants and all participants who are enrolled but never randomized (this is all enrolled (ie, consented) subjects.)

Pediatric Safety Set for OFCs- Stage 1 (PSS-OFC-S1): All PSS-S1 participants who have had at least one blinded OFC during the DBPCFC at the end of Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

Safety Set for OFCs - Stage 1 (SS-OFC-S1): All SS-S1 participants who have had at least one blinded OFC during the DBPCFC at the end of Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

Pediatric Pre-Randomization Safety Set for Screening OFCs - Stage 1 (PSS-PRERAND-OFC-S1): All PSS-PRERAND-S1 participants who have had at least one blinded OFC during the Screening DBPCFC.

Pre-Randomization Safety Set for Screening OFCs - Stage 1 (SS-PRERAND-OFC-S1): All SS-PRERAND-S1 participants who have had at least one blinded OFC during the Screening DBPCFC.

4.2. Stage 1 Open Label Extension Analysis Populations

Pediatric Full Analysis Set - Stage 1 OLE (PFA-S1OLE): All participants aged less than 18 years at randomization in Stage 1 who have moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.

Full Analysis Set- Stage 1 OLE (FA-S1OLE): All participants who have moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.

Pediatric Safety Set - Stage 1 OLE (PSS-S1OLE): All participants in the PFA-S1OLE population who have received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as "omalizumab" if a participant

received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.

Safety Set - Stage 1 OLE (SS-S1OLE): All participants who have moved to Stage 1 OLE and received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.

Pediatric Safety Set for OFCs - Stage 1 OLE (PSS-OFC-S1OLE): All PSS-S1OLE participants who have had at least one blinded OFC during the DBPCFC at the end of Stage 1 OLE, grouped according to treatment arm received in Stage 1 defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.

Safety Set for OFCs - Stage 1 OLE (SS-OFC-S1OLE): All SS-S1OLE participants who have had at least one blinded OFC during the DBPCFC at the end of Stage 1 OLE, grouped according to treatment arm received in Stage 1 defined as "omalizumab" if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

The disposition of all screened participants will be summarized in tables and listed. The following disposition information will be summarized:

- The number of participants screened.
- Among screened participants, the number and percentage of participants…
  - who failed Screening (including those that attended the initial Screening visit and/or the Screening DBPCFC, but did not meet the inclusion/exclusion criteria) and the reason for screen failure
  - who were placed on hold due to COVID-19 along with the study stage at time of hold (screening, stage 1, or stage 1 OLE)
  - in the PFA-S1
  - in the FA-S1
  - in the PPP-S1
  - in the PSS-S1
  - in the SS-S1
  - in the PSS-PRERAND-S1
  - in the SS-PRERAND-S1
  - in the PSS-OFC-S1
  - in the SS-OFC-S1
  - in the PSS-PRERAND-OFC-S1

  - in the SS-PRERAND-OFC-S1
  - in the PFA-S1OLE
  - in the FA-S1OLE
  - in the PSS-S1OLE
  - in the SS-S1OLE
  - in the PSS-OFC-S1OLE
  - in the SS-OFC-S1OLE

- Among participants in the PFA-S1 population and grouped by Stage 1 treatment arm, the number and percentage of participants…
  - who complete Stage 1
  - failed any inclusion/exclusion criteria (note: this is also a protocol deviation)
  - who withdrew during Stage 1 along with reason for withdrawal
  - who were placed on hold due to COVID-19 during Stage 1
  - with the food designated as a participant-specific food, for each of the six foods that may be used in this study as a participant-specific food (except peanut)
  - with the food designated as a participant-specific food who completed the blinded OFC to the food during the DBPCFC at the end of Stage 1, for each of the six foods that may be used in this study as a participant-specific food and peanut
  - in the PFA-S1
  - in the PPP-S1
  - in the PSS-S1
  - in the PSS-PRERAND-S1
  - in the PSS-OFC-S1
  - in the PSS-PRERAND-OFC-S1
  - in the PFA-S1OLE
  - in the PSS-S1OLE
  - in the PSS-OFC-S1OLE

- Among participants in the PPP-S1 population and grouped by Stage 1 treatment arm, the number and percentage of participants…
  - who complete Stage 1
  - who withdrew during Stage 1 along with reason for withdrawal
  - who were placed on hold due to COVID-19 during Stage 1
  - with the food designated as a participant-specific food, for each of the six foods that may be used in this study as a participant-specific food (except peanut),
  - with the food designated as a participant-specific food who completed the blinded OFC to the food during the DBPCFC at the end of Stage 1, for each of the six foods that may be used in this study as a participant-specific food (except peanut)

- Among participants in the PFA-S1OLE population, the number and percentage of participants…

- who complete Stage 1 OLE
- who withdrew during Stage 1OLE along with reason for withdrawal
- who were placed on hold due to COVID-19 during Stage 1 or Stage 1 OLE
- with the food designated as a participant-specific food, for each of the six foods that may be used in this study as a participant-specific food (except peanut),
- with the food designated as a participant-specific food who completed the blinded OFC to the food during the DBPCFC at the end of Stage 1 OLE, for each of the six foods that may be used in this study as a participant-specific food (except peanut)
- in the PSS-S1OLE
- in the PSS-OFC-S1OLE

Data listings of participant disposition and analysis population inclusion will be provided for the FA-S1 and FA-S1OLE populations separately. A separate listing of reason for exclusion from the PPP-S1 population will be provided for the PFA-S1.

For participants who restart a stage due to COVID-19 hold or other protocol-defined reasons, the study stage (Screening, Stage 1, or Stage 1 OLE) along with the dates of the hold and stage restart will be listed for the SS-PRERAND-S1 population.

For all participants that were screen failures or who failed an inclusion/exclusion criteria but who were otherwise randomized among the screened population, reason for screen failure and specific failed inclusion/exclusion criteria will be summarized and listed.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for demographic and baseline characteristics will be summarized in the PFA-S1 population grouped by randomized Stage 1 treatment arm and overall.

Demographic data will include age at randomization, sex, race, ethnicity, and CRU.

Baseline for Stage 1 (BLS1) will be defined as the last measurement prior to or on the day of randomization (beginning of Week 0 during Stage 1). Baseline characteristics will include:

- Body weight[1]
- Height[1]
- BMI[1]
- For each food, eliciting dose (mg) at which a participant experiences dose-limiting symptoms during the Screening DBPCFC will be summarized for the participants with each participant-specific food
- Skin prick test (SPT) wheal size ≥ 4 mm wheal greater than saline control for each of the seven foods that may be used during the DBPCFC (peanut, milk, egg, wheat, cashew, hazelnut, and walnut) will be summarized for the participants with each participant-specific food
- SPT wheal size > 3 mm wheal greater than saline control for each other allergen tested (food allergens: soy, sesame, almond, pecan, pistachio, and Brazil nut; environmental allergens: dust mite, cat, dog, Timothy grass, ragweed, oak, birch, Alternaria sp.)

- Self-reported history of food allergy for each food
- Specific IgE (kUA/L) ≥ 0.35 kUA/L for each food will be summarized for the participants with each participant-specific food
- SCORing Atopic Dermatitis (SCORAD) (among participants with atopic dermatitis)[2]
- Asthma severity (well controlled, partly controlled, or uncontrolled as assessed by GINA Guidelines, Protocol Appendix 3)
- Forced expiratory volume in one second (FEV_1) percent predicted in participants who are age seven years or older at Screening and able to perform spirometry
- FEV_1/forced vital capacity (FVC) in participants who are age seven years or older at Screening and able to perform spirometry
- Asthma Control Questionnaire (ACQ) for participants who are aged 11 years or older at Screening and unable to perform spirometry due to COVID-19
- Asthma Control Questionnaire (ACQ-IA) for participants who are aged 10 years or younger at Screening and unable to perform spirometry due to COVID-19
- Quality of life using the Food Allergy Quality of Life Questionnaire (FAQLQ) total score as well as each sub-domain[1]

[1]This measure is repeated upon restart of Stage 1 if a participant was put on hold and the repeated value will be listed separately.

[2]This measure is repeated upon restart of Screening DBPCFC if a participant was put on hold and the repeated value will be list separately.

For participants who restart Stage 1 or Screening DBPCFC due to COVID-19, the original baseline value prior to restart will be reported for the demographics and baseline characteristics. Any repeated baseline characteristics upon restart will be included in appropriate listings.

Summary descriptive statistics for demographic and baseline characteristics will also be summarized in the PFA-S1OLE population grouped by Stage 1 treatment arm and overall. Body habitus, self-reported food allergy, specific IgE, and eliciting dose during the blinded OFC to each food at the Screening DBPCFC will be summarized in the PFA-S1OLE population using data collected at BLS1. SPT results, SCORAD, asthma characteristics, and FAQLQ will be summarized in the PFA-S1OLE population using data collected at BLS1 as well as at the most recent measurement prior to or on the first injection of open label omalizumab during Stage 1 OLE.

Demographic and baseline characteristics will be summarized. Demographic and baseline characteristics in PFA-S1 population will also be compared between Stage 1 treatment arms using T-tests, Wilcoxon Sign-Rank Tests, or Chi-Square Tests, as applicable. Resulting p-values from these tests are intended to be strictly descriptive and not inferential.

A data listing of demographics, baseline characteristics, and medical history will be provided for the FA-S1 population.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Protocol deviations during Screening, Stage 1, and Stage 1 OLE will be recorded on the protocol deviation electronic case report form (eCRF) page. Major protocol deviations will be identified by the DAIT Medical Monitor and study team prior to unblinding of treatment assignment and database freeze. This review will also identify deviations that will exclude participants from PPP-S1, defined as major protocol deviations that could be expected to materially affect efficacy during Stage 1. These deviations will include:

- Participants randomized to Stage 1 despite not meeting inclusion/exclusion
- Participants who had an AE during Stage 1 that qualified for discontinuation but were not discontinued
- Participants who did not sign informed consent
- Participants who met a participant stopping rule (see protocol) that should have resulted in removal of the participant from the study, but the participant remained in the study

A listing will be provided for protocol deviations across screening, Stage 1 and Stage 1 OLE for participants in the SS-PRERAND-S1 population. The listing will be sorted by CRU, age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, and participant ID and will also include category of deviation, severity of the deviation (major or non-major), date of occurrence, and the deviation description. A separate listing of Protocol Deviations associated with COVID-19 will also be provided.

Protocol deviations in Screening for the PSS-PRERAND-S1 population will be summarized separately by CRU and by type of deviation (including the major deviations listed above).

Protocol deviations in Stage 1 for the PSS-S1 population will be summarized separately by CRU and by type of deviation (including the major deviations listed above).

Protocol deviations in Stage 1 OLE for the PSS-S1OLE population will be summarized separately by CRU and by type of deviation (including the major deviations listed above).

6.2. Compliance

The percentage of expected doses received will be summarized in the PFA-S1 population to assess compliance with study drug dosing regimen. The percentage of expected doses will be defined as the number of doses received divided by the total number of expected doses for the entire stage based on assigned dosing frequency.

Compliance will be listed in the Exposure Listings noted in Section 6.3.

6.3. Exposure

The number and percentage of participants receiving each scheduled injection (i.e, dose) of study drug (omalizumab and placebo for omalizumab), each injection schedule (every 2 week or every 4

weeks), and dose level received (75mg, 150mg, 225mg, etc.) for each of the 2 schedules will be summarized by treatment arm.

The overall duration of exposure (weeks) will be summarized descriptive as a continuous variable also by the number of participants and percentage categorically (i.e., ≥4 – 8 weeks, ≥8 – 12 weeks, etc). Duration of total exposure will be defined based on the difference (in days) between the dates of the first and last dose of study drug plus 1 day for each study period. For participants who restarted Stage 1 or Stage 1 OLE, the total duration of exposure will include the time between the first exposure (before hold) through the last exposure (after restart). Therefore, this window will also include the duration of the hold itself. Exposure duration will also be calculated and summarized ignoring dosing prior to restarting a stage for participant placed on hold.

Stage 1 exposure will be summarized for the PSS-S1 population with Stage 1, Stage 1 OLE, and the combination of Stage 1 and Stage 1 OLE summarized for the PSS-S1OLE population.

A data listing will be provided separately for extent of exposure and compliance during Stage 1 for the SS-S1 population, extent of exposure during Stage 1 OLE for the SS-S1OLE population, and extent of exposure during Stage 1 and Stage 1 OLE combined for the SS-S1OLE population.

7. ENDPOINT EVALUATION

7.1. Overview of Efficacy Analysis Methods

Hypothesis testing for all efficacy endpoints will be performed in the PFA-S1 or PFA-S1OLE populations as appropriate.

A data listing of efficacy endpoints based on the blinded OFC to each food during the DBPCFC at the end of Stage 1 (including consumption without dose-limiting symptoms at each threshold as well as the maximum tolerated dose without dose-limiting symptoms) will be provided for the FA-S1 population. Similarly, a data listing of efficacy endpoints based on the blinded OFC to each food during the DBPCFC at the end of Stage 1 OLE will be provided for the FA-S1OLE population. All efficacy listings will be sorted by age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, participant ID, and food.

7.1.1. Handling of Dropouts or Missing Data

For the primary analysis, if a participant does not complete a blinded OFC to a food during the DBPCFC at the end of Stage 1 or Stage 1 OLE because the participant is withdrawn from the study prior to the OFC (see protocol) or the participant misses the visit where a blinded OFC would be performed, the participant will be considered a 'failure' for all efficacy endpoints based on the blinded OFC that was missed. For these participants, the maximum tolerated dose without dose-limiting symptoms will also be set to 0 mg.

If a participant stops an OFC to a food before the participant has consumed the final dose in the OFC and does not have dose-limiting symptoms on the last dose consumed (referred to as an indeterminate challenge), the participant will be considered a:

- 'Success' if the participant consumed the dose that is used to define the efficacy endpoint; or
- 'Failure' if the participant did not consume the dose that is used to define the efficacy endpoint.

If a participant has dose-limiting symptoms at any dose of the blinded OFC to placebo, the participant will be considered a 'failure' at every dose of the blinded OFCs to peanut and two other participant-specific foods.

If a participant stops the blinded OFC to placebo at any point or does not have the blinded OFC to placebo, the participant will be considered a 'failure' at every dose of the blinded OFCs to peanut and two other participant-specific foods.

For example, suppose a participant consumes a single dose of 600 mg of peanut protein without dose-limiting symptoms but then refuses to continue with the OFC at the end of Stage 1. In this case, the participant will be assumed to have met the primary endpoint but they will be marked as a failure for efficacy endpoints defined by consumption of a single dose of ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg peanut protein without dose-limiting symptoms during the blinded OFC at the end of Stage 1. Imputation of missing DBPCFC data in this way assumes that the data is missing-not-at-random (MNAR). To assess the impact of the MNAR assumption, a sensitivity analysis of the primary endpoint will be performed (see Section 7.3.3).

For FAQLQ and immune biomarker endpoints, any missing data will be assumed MAR and no explicit imputation will be performed.

7.1.2. Multicenter Studies

Participants will be recruited from ten clinical research units (CRUs). Sub-group analyses of the primary endpoint will be performed using each CRU as a sub-group (see Section 7.3.3).

7.1.3. Assessment Time Windows

Visit windows for all scheduled visits are provided in the protocol. Injection or dosing visits for study drug will be allowed to occur +/-1 day outside of the specified visit window. Based on PI discretion, a DBPCFC visit may also occur outside of the specified visit window. A visit that occurs outside of the specified visit window will be recorded as a protocol deviation. Any data collected outside of a visit window will still be included in any analyses of the scheduled visit.

Summaries of vital signs, growth parameters, limited physical exam, diet and allergy questionnaire, and GI symptoms questionnaire will be performed by visit. If multiple visits occur within an injection or dosing visit window, the results recorded at the dosing visit will be used for

any by-visit summaries . All records will be included in listings regardless of whether or not they occurred at the time of dosing.

All DBPCFC endpoints will be summarized by food rather than visit. For example, the results of all blinded OFCs to peanut will be summarized together, regardless of the week it was performed.

7.1.4. Endpoints and Analysis Methods

Table 7.1.4 provides a summary of planned analysis methods for primary and secondary endpoints in Stage 1 and Stage 1 OLE. Addition details of efficacy analyses, including exploratory analyses, are included in Sections 7.3-7.5.

Participants who restart a stage will only be counted once for analyses of that stage.

For all efficacy analyses for Stage 1 OLE, a separate analysis will be performed for 1) all PFA-S1OLE participants, and 2) PFA-S1OLE participants who did not restart Stage 1 OLE.

A participant will only be included in analyses of OFC endpoints and allergen-specific immune biomarkers (allergen-specific IgE, allergen-specific IgG4, allergen-specific IgA, basophil activation, and SPTs) for peanut and the two other participant-specific foods determined at Screening. That is, participants will not be included in analyses for other food not determined to be participant-specific foods at screening.

Table 7.1.4 Endpoints and Analysis Methods for Primary and Secondary Endpoints

Endpoint	Data Source	Fisher's Exact Test	Exact Logistic Regression Model	Ordinal Logistic Regression Model	Descriptive Analysis[c]
Primary Endpoint					
Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	DBPCFC at the end of Stage 1	PFA-S1[a], PPP-S1[b], FA-S1[b]	PFA-S1[b], FA-S1[b]	---	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE
Key Secondary Endpoints					
Consumption of a single dose of ≥1000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 for each of the following: • Cashew • Milk • Egg	DBPCFC at the end of Stage 1	PFA-S1[a]	PFA-S1[c]	---	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE
Other Secondary Endpoints					
Secondary Endpoint 5-1 – 5-6, 5-9 – 5-12, 5-15 – 5-21, 5-24 – 5-30. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints).[c]	DBPCFC at the end of Stage 1	PFA-S1[]	---	---	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE
Secondary Endpoint 5-7, 5-13, 5-22, 5-31. In at least two foods, consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1.[c]	DBPCFC at the end of Stage 1	PFA-S1[]	---	---	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE

Endpoint	Data Source	Fisher's Exact Test	Exact Logistic Regression Model	Ordinal Logistic Regression Model	Descriptive Analysis[c]
Secondary Endpoint 5-8, 5-14, 5-23, 5-32. In all three foods, consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1. [c]	DBPCFC at the end of Stage 1	PFA-S1[]	---	---	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE
Secondary Endpoint 6-1 – 6-4. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	DBPCFC at the end of Stage 1	---	---	PFA-S1	PFA-S1OLE using DBPCFC at the end of Stage 1 OLE

[a] Under Type I error control (described in Section 7.2).
[b] Supporting analysis per Section 7.3.3.
[c] Each dose/food combination is a separate endpoint to be analyzed separately. See Section 14.1 for a complete list of endpoints.

7.2. Type I Error Control

To control the inflation of Type I error that arises when multiple tests of comparison are performed within and across multiple families of endpoints (i.e., the primary endpoint as well as Stage 1 key secondary endpoints), both gatekeeping and multiple testing strategies will be performed to ensure the overall family-wise error rate is ≤ 5%. All hypotheses testing under Type I error control will be performed in the PFA-S1 population.

Interim Analysis

At interim (N=165), efficacy would be declared only if the two-sided p-value for the peanut is significant at $p < 0.0001$ and the two-sided p-values for all secondary foods (cashew, milk, and egg) are significant at $p < 0.005$, with all p-values being significant in the right direction (i.e., favoring omalizumab).

Final Analysis

If the interim analysis is unsuccessful, the final analysis will be performed (planned N=210). At the final analysis, the primary endpoint will be tested using the full α of 0.05, considering the α of 0.0001 from the interim analysis to be trivial, and key secondary endpoints tested will be tested at an α of 0.0497 after using 0.005 at interim with 79% of information (165/210). A gatekeeping approach will be followed that incorporates looking back to interim analysis for p-values of specific foods to determine if the next gate will be open or closed. The hierarchy for testing is as follows: I) peanut, II) cashew, III) egg, and IV) milk. For testing a specific allergen, all previous allergen(s) must be successful where success criteria are defined below:

(I) **Peanut:** successful if peanut significant at interim ($p<0.0001$) OR at final ($p<0.05$)

(II) **Cashew:** successful if peanut is successful AND cashew is significant at either the interim ($p<0.005$) OR final ($p<0.0497$)

(III) **Egg:** successful if peanut and cashew are successful AND egg is significant at either the interim ($p<0.005$) OR final ($p<0.0497$)

(IV) **Milk:** successful if peanut, cashew, and egg are successful AND milk is significant at either the interim ($p<0.005$) OR final ($p<0.0497$)

7.3. Primary Endpoint

7.3.1. Computation of the Primary Endpoint

After 16 weeks of treatment, each participant will complete a DBPCFC (see protocol) consisting of placebo and each of their three participant-specific foods to a cumulative dose of 6044 mg protein of each food. Challenges may occur over four separate visits to accommodate challenges for three foods and placebo. Each participant will continue to receive omalizumab or placebo for omalizumab injections until all challenges are completed. All challenges must occur within a maximum period of 28 days and so Stage 1 may last between 16 and 20 weeks.

The primary endpoint is consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. A participant who meets this endpoint will be considered a 'success' while a participant who does not meet this endpoint will be considered a 'failure'. Missing data for the primary endpoint will be assumed MNAR and imputed, as described in Section 7.1.1.

7.3.2. Primary Analysis of the Primary Endpoint

The primary analysis of the primary endpoint is designed to test the following hypotheses:

- Null hypothesis: The odds a participant consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in omalizumab and placebo for omalizumab arms are equal.
- Alternative hypothesis: The odds a participant consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in omalizumab and placebo for omalizumab arms are not equal.

The main estimand for the primary endpoint is defined as follows:

Treatment: The estimand is intended to provide an estimate of the treatment effect of omalizumab in comparison to placebo for omalizumab.

Population: All participants who have been randomized to receive either omalizumab or placebo for omalizumab in Stage 1 (PFA-S1 population). Participants will be analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment they actually received in Stage 1.

Variable: A binary response based on the consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. A participant who meets this endpoint will be considered a 'success' while a participant who does not meet this endpoint will be considered a 'failure'.

Intercurrent events: All intercurrent events including death, stopping the blinded OFC to peanut prior to the 600 mg dose, having dose-limiting symptoms at any dose of the blinded OFC to placebo, and stopping the blinded OFC to placebo at any dose, will be handled following the composite strategy, i.e., the participant will be considered as 'failure' for the primary endpoint. Participants who discontinue treatment will be withdrawn and therefore also will be considered "failure" for any missing endpoints. For further details regarding missing data (including participant withdrawal), refer to Section 7.1.1.

Population-level summary: The odds ratio comparing consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 between the omalizumab and placebo for omalizumab arms.

The primary analysis of the primary endpoint will use Fisher's exact test to compare the omalizumab and placebo for omalizumab arms with respect to the proportion of participants that consume a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. The null hypothesis will be tested using a two-sided significance level of 0.0001 at the interim analysis and, assuming the study continues beyond the interim analysis, at 0.05 for the final analysis. Both the odds ratio and the difference in proportions (and associated 95% exact clopper-pearson confidence interval for each) comparing consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms between the omalizumab and placebo for omalizumab arms will be reported.

7.3.3. Supportive Analyses of the Primary Endpoint

Supportive analyses of the primary endpoint are described below.

Sensitivity Analyses:

1. A tipping point analysis of the primary endpoint will also be performed to assess the sensitivity of results to the MNAR assumption3.
2. If more than 2 participants have an imputed primary endpoint due to not having the blinded OFC to placebo, a sensitivity analysis of the primary endpoint will be performed using the observed outcome of the blinded OFC to peanut.

Supplementary Analyses:

1. The primary endpoint will also be analyzed using exact logistic regression to model the log odds a participant consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. The model will include the following fixed effects based on randomization: treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1. The adjusted proportion (and associated standard error and 95% confidence interval) in each treatment arm will be reported. The odds ratio (and associated 95% exact confidence interval) comparing consumption of a single dose of

≥600 mg of peanut protein without dose-limiting symptoms between the omalizumab and placebo for omalizumab arms will be reported.

2. Analysis of the primary endpoint will be replicated using both the PPP-S1 population and the FA-S1 population.
3. Separate subgroup analyses of the primary analysis for the primary endpoint will be conducted using the PFA-S1 population. Subgroups will be defined by: 1) age at Stage 1 randomization (<6, 6 to <12, 12 to <18); 2) order of blinded OFC to peanut during the DBPCFC at the end of Stage 1; 3) race; 4) ethnicity; 5) sex; 6) CRU; 7) dose consumed during the Screening DBPCFC with dose-limiting symptoms (≤30 mg or 100 mg of peanut protein); and 8) omalizumab dosing frequency (2 or 4 weeks). For each subgroup analysis, odds ratios and 95% exact confidence intervals will be displayed in a forest plot.
4. Separate analysis excluding participants who had dose-limiting symptoms to the 300 mg dose of placebo used in the blinded OFC to peanut during the Screening DBPCFC from the PFA-S1 population. This analysis will fit an exact logistic regression model similar to that described in supplementary analysis #1.
5. Separate analysis excluding participants who restarted Stage 1 from the PFA-S1 population. This analysis will fit an exact logistic regression similar to that described in supplementary analysis #1.
6. To predict the probability of consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 using each immune biomarker measured at the first Screening DBPCFC Visit, a least absolute shrinkage and selection operator (LASSO) model will be developed. Only Stage 1 treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1 will be forced into the model as covariates. All immune biomarker levels measured at the first Screening DBPCFC Visit and the interaction between each immune biomarker and Stage 1 treatment arm will be included as possible covariates. Covariates will be log transformed, as appropriate. Five-fold cross-validation will be used to estimate the average square error of possible models and the model with the lowest average square error will be selected. This analysis will be performed using the glmnet package from R (Version 3.5).

7.4. Secondary Endpoints

7.4.1. Key Secondary Endpoints

The significance level used for key secondary endpoints and the approach of controlling family-wise Type I error rate (at 5% level) are described in Section 7.2.

7.4.1.1. Secondary Endpoint 1

Endpoint: Consumption of a single dose of ≥1000 mg cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

The estimand for this endpoint is similar to that of the primary endpoint except the binary outcome relates to dose of ≥1000 mg of cashew protein (rather than ≥600 mg of peanut protein).

Analysis: Consumption of a single dose of ≥1000 mg cashew protein without dose-limiting symptoms will be evaluated by applying a Fisher's exact test (similar to Section 7.3.2). The null hypothesis will be tested using a two-sided significance level of 0.005 at the interim analysis and, assuming the study continues beyond the interim analysis, at 0.0497 for the final analysis

7.4.1.2. Secondary Endpoint 2

Endpoint: Consumption of a single dose of ≥1000 mg milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

The estimand for this endpoint is similar to that of the primary endpoint except the binary outcome relates to dose of ≥1000 mg of milk protein (rather than ≥600 mg of peanut protein).

Analysis: Consumption of a single dose of ≥1000 mg milk protein without dose-limiting symptoms will be evaluated by applying a Fisher's exact test (similar to Section 7.3.2). The null hypothesis will be tested using a two-sided significance level of 0.005 at the interim analysis and, assuming the study continues beyond the interim analysis, at 0.0497 for the final analysis

7.4.1.3. Secondary Endpoint 3

Endpoint: Consumption of a single dose of ≥1000 mg egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

The estimand for this endpoint is similar to that of the primary endpoint except the binary outcome relates to dose of ≥1000 mg of egg protein (rather than ≥600 mg of peanut protein).

Analysis: Consumption of a single dose of ≥1000 mg egg protein without dose-limiting symptoms will be evaluated by applying a Fisher's exact test (similar to Section 7.3.2). The null hypothesis will be tested using a two-sided significance level of 0.005 at the interim analysis and, assuming the study continues beyond the interim analysis, at 0.0497 for the final analysis

7.4.2. Other Secondary Endpoints

7.4.2.1. Secondary Endpoint 5-1 – 5-32

Endpoint: Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints in Stage 1). For a list of endpoints defined by Secondary Endpoint 5, see Section 14.1.

Analysis: Using the PFA-S1 population and subgroups according to each food as appropriate, each endpoint will be separately analyzed using a Fisher's exact test (similar to Section 7.3.2).

A two-sided significance level of 0.05 will be applied to each endpoint. No multiple comparison adjustment will be applied to this test.

7.4.2.2. Secondary Endpoint 6-1 – 6-4

Endpoint: Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

Analysis: Using the PFA-S1 population, each endpoint will be analyzed using an ordinal logistic regression model. The model will include fixed effects given by treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1. The odds ratio (and associated 95% Wald confidence interval) comparing consumption of a higher number of foods without dose-limiting symptoms between the omalizumab and placebo for omalizumab arms will be reported. Hypotheses will be tested using a Wald chi-square Type III test of the effect of treatment arm obtained from the model and a two-sided significance level of 0.05 will be used.

This statistical model assumes proportional odds and so this assumption will be tested during the analysis using a score test (PROC LOGISTIC, SAS Version 9.3). If the proportionality assumption fails, a generalized logit model will be used instead of the ordinal logistic model. In this case, the odds ratios (and associated 95% Wald confidence intervals) of consuming 0 versus 1, 1 versus 2, and 2 versus 3 foods without dose-limiting symptoms between the omalizumab and placebo for omalizumab arms will be reported. Hypotheses will be tested using a Wald chi-square Type III test of the effect of treatment arm obtained from the model and a two-sided significance level of 0.05 will be used.

7.4.3. Supportive Analyses of Secondary Endpoints

Supportive analysis of secondary endpoints will include:

Sensitivity analyses:

1. If more than 2 participants have an imputed endpoint due to not having the blinded OFC to placebo, a sensitivity analysis of each secondary endpoint will be performed using the observed outcome of the blinded OFC for that endpoint.

Supplementary analyses:

2. To assess sensitivity of results to analysis population, replication of the analyses of the key secondary endpoints and the secondary endpoint corresponding to ≥1000 mg of peanut protein (Secondary Endpoint #5-9) using the FA-S1 population.
3. For the key secondary endpoints measured in Stage 1, each analysis will be performed excluding participants who restarted Stage 1 for any reason (including due to COVID-19) from the PFA-S1 population.

4. Separate subgroup analyses of the key secondary endpoints will be conducted using the PFA-S1 population. Subgroups will be defined by: 1) age at Stage 1 randomization (<6, 6 to <12, 12 to <18); 2) order of blinded OFC to peanut during the DBPCFC at the end of Stage 1; 3) race; 4) ethnicity; 5) sex; 6) CRU; 7) dose consumed during the Screening DBPCFC with dose-limiting symptoms (≤30 mg or 100 mg of peanut protein); and 8) omalizumab dosing frequency (2 or 4 weeks). For each subgroup analysis, odds ratios and 95% exact confidence intervals will be displayed in a forest plot.
5. To predict the probability of consuming a single dose of ≥1000 mg protein of the food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 for each food other than peanut using each immune biomarker measured at the first Screening DBPCFC Visit, a LASSO model will be developed. Only Stage 1 treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1 will be forced into the model as covariates. Milk as a participant-specific food (yes/no) will not be included as a fixed effect for the model applied to the milk endpoint. All immune biomarker levels measured at the first Screening DBPCFC Visit and the interaction between each immune biomarker and Stage 1 treatment arm will be included as possible covariates. Covariates will be log transformed, as appropriate. Five-fold cross-validation will be used to estimate the average square error of possible models and the model with the lowest average square error will be selected. This analysis will be performed using the glmnet package from R (Version 3.5).

7.5. Exploratory Endpoints

Exploratory endpoints measured in Stage 1 and Stage 1 OLE will be analyzed using the PFA-S1 and PFA-S1OLE populations, respectively. All analyses will be based on a two-sided significance level of 0.05; 95% confidence intervals of the appropriate endpoint estimate will also be reported.

7.5.1. Exploratory Endpoint 2-1 – 2-45

Endpoint: Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.

Analysis: Using the PFA-S1OLE population and subgroups according to each food, each endpoint measured during the DBPCFC at the end of Stage 1 and Stage 1 OLE will be summarized using descriptive statistics (see Section 3). For each food, shift tables of each endpoint measured at the end of Stage 1 OLE by the endpoint measured at the end of Stage 1 will be presented by treatment arm.

7.5.2. Exploratory Endpoint 3-1 – 3-5

Endpoint: Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.

Analysis: Using the PFA-S1OLE population, the proportion of participants consuming 0, 1, 2, or 3 foods at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 and Stage 1 OLE will be summarized using descriptive statistics (see Section 3). Shift tables of the number of foods consumed at a single dose of ≥1000 mg without dose-limiting symptoms at the end of Stage 1 OLE by the number of foods consumed at a single dose of ≥1000 mg without dose-limiting symptoms at the end of Stage 1 will be presented by treatment arm.

7.5.3. Exploratory Endpoint 4-1 – 4-4

Endpoint: Change in quality of life between Week 0 in Stage 1 (BLS1) and the following times:

- First DBPCFC visit at the end of Stage 1;
- For those participants who move to Stage 1 OLE:
  - Beginning of Stage 1 OLE;
  - First DBPCFC visit at the end of Stage 1 OLE; and
  - Last DBPCFC visit at the end of Stage 1 OLE.

Quality of life is measured by the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) for participants aged 0-12 years, Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) for children/adolescents aged 8-12 years, Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) for participants aged 13-17 years, and Food Allergy Quality of Life Questionnaire – Adult Form (FAQLQ-AF) for participants aged ≥18 years.

Analysis: Change in quality of life (total score as well as each sub-domain) between Week 0 in Stage 1 and the first DBPCFC visit at the end of Stage 1 will be analyzed using a linear mixed model that will include a random intercept and fixed effects for Stage 1 treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), time of measurement (baseline or first DBPCFC visit at the end of Stage 1), and an interaction term between treatment arm and time of measurement. For each sub-domain, a separate model will be fit for each form type (FAQLQ-PF, FAQLQ-CF, etc.) and subdomain. The model will be fit using restricted maximum likelihood and each fixed effect will be tested using an F-test statistic, the Kenward-Roger approximation for degrees of freedom, and a two-sided significance level of 0.05. The model will also be used to estimate the following:

- The mean difference in quality of life over time in each treatment arm.
- The difference in mean differences in the quality of life over time between treatment arms.

The mean difference in quality of life between BLS1 and the first DBPCFC visit at the end of Stage 1, the first dosing visit in Stage 1 OLE, and the first and last DBPCFC visit at the end of Stage 1 OLE will be summarized in the PFA-S1OLE population using descriptive statistics (see Section 3).

7.5.4. Exploratory Endpoints 8 – 12

Endpoint: Biomarkers include the following:

- 8-1 – 8-14. Allergen-specific IgE
- 9-1 – 9-14. Allergen-specific immunoglobulin G4 (IgG4)
- 10-1 – 10-14. Allergen-specific immunoglobulin A (IgA)
- 11-1 – 11-14. IgG4/IgE ratio
- 12-1 – 12-14. Basophil activation

Allergen-specific immune biomarkers (allergen-specific IgE, allergen-specific IgG4, allergen-specific IgA, and basophil activation) will be evaluated using peanut and two other participant-specific foods.

These immune biomarkers will be measured at the following times:

- Baseline (first Screening DBPCFC Visit, BLS1);
- First DBPCFC visit at the end of Stage 1; and
- First DBPCFC visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE).

Analysis: Each log-transformed immune biomarker will be modeled using a linear (or nonlinear, if appropriate) mixed model (similar to Section 7.5.3) that will include a random intercept and fixed effects for treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), time of measurement (BLS1 or first DBPCFC visit at the end of Stage 1), and an interaction term between treatment arm and time of measurement. The model will be used to estimate the following:

- The geometric mean ratio of the immune biomarker over time in each treatment arm.
- The geometric mean ratio of the geometric mean ratio in the immune biomarker over time between treatment arms.

The change in immune biomarkers between BLS1 and the first DBPCFC visit at the end of Stage 1 and between BLS1 and the first DBPCFC visit at the end of Stage 1 OLE will be summarized in the PFA-S1OLE population using geometric mean ratio, geometric standard deviation, and the number of participants.

7.5.5. Exploratory Endpoint 13-1 – 13-14

Endpoint: Wheal size of SPT to peanut and two other participant-specific foods at baseline (at the Screening DBPCFC Visit, BLS1), the first DBPCFC visit at the end of Stage 1, and the first DBPCFC visit at the end of Stage 1 OLE.

Analysis: Wheal size of SPT for each food at the first DBPCFC visit at the end of Stage 1 will be modeled using a linear (or nonlinear, if appropriate) mixed model (similar to Section 7.5.3) that will include a random intercept and fixed effects for treatment arm, age at randomization (<6

years versus ≥6 years), milk as a participant-specific food (yes/no), time of measurement (BLS1 or first DBPCFC visit at the end of Stage 1), and an interaction term between treatment arm and time of measurement. If the distribution of SPT wheal size is skewed, the square root of the endpoint will be used. The model will be used to estimate the following:

- The mean difference in the SPT wheal size over time in each treatment arm.
- The difference in mean differences in the SPT wheal size over time between treatment arms.

The mean difference in SPT wheal size between BLS1 and the first DBPCFC visit at the end of Stage 1 and between BLS1 and the first DBPCFC visit at the end of Stage 1 OLE will be summarized in the PFA-S1OLE population using descriptive statistics (see Section 3).

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

The safety analyses will be performed in the applicable safety analysis population defined in Section 4 (PSS-PRERAND-S1, PSS-S1, and PSS-S1OLE). Safety assessment summaries, as defined in the protocol, will include:

- Adverse events (AEs)
- Adverse events related to study drug
- Adverse events of special interest (AESIs)
- AEs leading to discontinuation of study drug
- Serious adverse events (SAEs)
- Deaths
- Clinical laboratory results
- Vital signs
- Physical examinations

These analyses will not be stratified by CRU.

Any AE occurring after signing of the informed consent but prior to the initiation of omalizumab or placebo for omalizumab will be considered a non-treatment emergent. These events will be summarized in the PSS-PRERAND-S1 and listed for the SS-PRERAND-S1 population.

A treatment-emergent adverse event (TEAE) will be defined as any AE not present prior to the initiation of study drug or any AE already present that worsens in either intensity or frequency following exposure to study drug. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc. during treatment periods will be considered a treatment-emergent AE. TEAEs will be summarized in the PSS-S1 and PSS-S1OLE populations and listed for the SS-S1 and SS-S1OLE populations, as applicable.

Treatment-emergent AEs will be recorded as follows:

TEAE – Stage 1: Any AE not present prior to the initiation of omalizumab or placebo for omalizumab and occurring prior to either the first injection of open label omalizumab in Stage 1 OLE for participants moving to Stage 1 OLE or the first injection of open label omalizumab in Stage 2 for participants moving to Stage 2. If an AE occurs on the same day as the first injection of omalizumab or placebo for omalizumab in Stage 1, it will be considered a TEAE – Stage 1. If an AE occurs on the same day as the first injection of open label omalizumab in Stage 2, it will be considered a TEAE – Stage 2.

TEAE – Stage 1 OLE: Any AE occurring after the first injection in Stage 1 OLE and prior to either the initial open feeding or initial dose escalation in Stage 3. If an AE occurs on the same day as the first injection of open label omalizumab in Stage 1 OLE, it will be considered a TEAE – Stage 1 OLE. If an AE occurs on the same day as an open feeding or IDE in Stage 3, it will be considered a TEAE – Stage 3.

Safety data will not be imputed, except for partial and missing dates, which will be imputed only for defining TEAEs. Imputed dates will not be presented in data listings.

Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless: 1) the first day of the month is before the date of administration of study drug and the month and year are the same as the month and year of the date of administration of study drug; and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day will be set to the day of administration of study drug.
- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless: 1) January 1st is before the date of administration of study drug and the year is the same as the year of the date of administration of study drug; and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day and month will be set to that of the date of administration of study drug.
- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the participant, in which case the end day will be set to that of the participant's last contact date.
- For a missing end day and month where the year is present, the end day and month will be set to the participant's last contact date, unless the year of the participant's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.

Unless otherwise specified, a data listing for all measurements in Section 8 will be provided for the SS-S1 population (with indicators for inclusion in SS-S1OLE population) and sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, participant ID, and time of assessment (e.g., visit, time, and/or event).

8.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA]). The latest edition of MedDRA will be used at the time of classification.

The severity of AEs will be classified, as applicable, using the following grading scales as defined in the protocol:

- Non-allergic AEs will be classified using the Grading Table for Non-Allergic Adverse Events (see protocol Appendix, titled Grading Table for Non-Allergic Adverse Events).
- AEs coded as systemic allergic reactions other than local reactions to skin prick testing will be classified using the CoFAR Grading Scale for System Allergic Reactions (see protocol, Section 12.4).
- AEs coded as local reactions to skin prick testing will be classified using the Grading Scale for Local Reactions to Skin Prick Testing (see Protocol, Section 12.4).

Each AE will be entered on the electronic case report form (eCRF) once at the highest severity. That is, if an AE becomes more severe, then the severity of the event will be updated in the eCRF.

The relationship, or attribution, of an AE to the study therapy regimen (i.e., study drug for Stage 1 and Stage 1 OLE) or study procedures is defined in the protocol.

8.2.1. Overall AE Summaries

Overall summary tables will be developed using the PSS-PRERAND-S1, PSS-S1, and PSS-S1OLE populations separately to report the number of events and the number and percentage of participants having at least one event in the following categories:

- AEs
- AEs by maximum grade
- AEs by relationship to study procedures
- AEs by relationship to study drug

These overall summary tables will be repeated excluding any AEs recorded during partial stages completed prior to a participant restarting a stage.

An additional overall AE summary table will be provided, including participants in the youngest age group (i.e., age 1-6).

8.2.2. AEs by System Organ Class and Preferred Term

AEs classified by Stage 1 treatment arm, MedDRA SOC and preferred term will be summarized in the PSS-S1 (for AEs in Stage 1) and PSS-S1OLE (for AEs in Stage 1 OLE and AEs in either Stage 1 or Stage 1 OLE) populations for each of the following categories:

- AEs

- AEs by maximum grade
- AEs relationship to study drug

Summary tables will present the total number of events as well as the number and percentage of participants (incidence rate) experiencing the events and the risk difference between treatment arms. If a participant experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of participants experiencing the events, a participant will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of participants in the specified safety population.

Similar summaries will be generated for AESIs (defined in the protocol) and AEs leading to discontinuation of study drug separately.

Data listings will be provided separately for AEs, AESIs, AEs leading to discontinuation of study drug, AEs occurring in participants ages 1-6 years-old, and cases of COVID-19. In the COVID-19 listings, AEs belonging to a participant with a confirmed case of COVID-19 will be included if the start date of the AE is up to seven days prior to the start of COVID-19 through 30-days after the start of COVID-19 or through the end of Stage 1/ Stage 1 OLE participation, whichever comes first. The listings will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and will be based on the SS-PRERAND-S1 population.

8.2.3. Forest Plots of AEs

A forest plot will be created based on the PSS-S1 population showing percentage of participants having at least one event in the given category during Stage 1 along with the risk difference and associated 95% confidence intervals comparing treatment groups.

Summary level:

1. All AEs
2. All AEs related to blinded omalizumab/placebo for omalizumab injection
3. All AEs related to blinded OFCs
4. All SAEs
5. All SAEs related to blinded omalizumab/placebo for omalizumab injection
6. All SAEs related to blinded OFCs
7. AEs of special interest
8. AEs of special interest related to blinded OFC
9. AEs leading to discontinuation
10. AEs leading to discontinuation related to blinded OFC

PT level:

1. AE with the most frequent preferred terms (occurring at least 5% of participants in either treatment group or in the combined population)

8.2.4. AEs Related to Blinded OFCs

Similar summary tables will be developed to report the number of events and the number and percentage of participants having at least one event in the following categories:

- AEs related to blinded OFCs during the Screening DBPCFC in the PSS-PRERAND-OFC-S1 population.
- AEs related to blinded OFCs during the Screening DBPCFC or DBPCFC at the end of Stage 1 in the PSS-OFC-S1 population.
- AEs related to blinded OFCs during the Screening DBPCFC, DBPCFC at the end of Stage 1, or DBPCFC at the end of Stage 1 OLE in the PSS-OFC-S1OLE population.

An additional table will be made for each of the previous event subsets related to blinded OFCs by stratifying AEs by those that occurred prior to Protocol V2.0 and those that occurred on or after Protocol V2.0.

- Additionally, a data listing will also be provided for all AEs related to blinded OFCs for the SS-PRERAND-OFC-S1 population, including all AEs related to blinded OFCs during the Screening DBPCFC, DBPCFC at the end of Stage 1, or DBPCFC at the end of Stage 1 OLE.

The supporting listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and include an indication of inclusion in the SS-OFC-S1 and/or SS-OFC-S1OLE populations.

8.2.5. Risks Associated with Omalizumab and Definitions

The following risks associated with omalizumab will be summarized separately using the specific definitions:

- Serum Sickness Syndrome/Serum Sickness Like Disease (SSLD) (PTs “Serum sickness” and “Serum sickness-like reaction”)
- Antibody formation to omalizumab (PTs “Drug specific antibody present”, “Human anti-human antibody test”, and “Drug specific antibody”)

The following risks associated with omalizumab will be first using the specified definitions. Events will be evaluated by the DAIT Medical Monitor and only confirmed events will be summarized. Events identified by the broad search criteria will be listed with the events confirmed by the DAIT Medical Monitor flagged:

- Churg Strauss Syndrome (CSS)/Hyper Eosinophilic Syndrome (HES)/Eosinophilic Granulomatosis with Polyangiitis (EGPA) (broad search criteria: MedDRA High Level Group Term (HLGT) “Vascular infections and inflammations” and MedDRA High Level Term (HLT) “Eosinophilic disorders”)

- Thrombocytopenia (SMQ [Standardized MedDRA Query] "Haematopoietic thrombocytopenia" [broad search criteria] and PT "Immune thrombocytopenia"
- Arterial Thrombotic Events (ATEs) (SMQs [broad search criteria]: "Myocardial Infarction" and "Other ischaemic heart disease", SMQs [narrow]: "Ischaemic central nervous system vascular conditions", "Haemorrhagic central nervous system vascular conditions" and PTs "Hemiparesis", "Hemiplegia", "Sudden cardiac death", "Sudden death", "Cardiac death", and "Arrhythmic storm")
- Malignant neoplasms (SMQ "Malignancies" [broad search criteria])

In addition to these risks, parasitic infections (broad search criteria: the MedDRA HLGT of "Helminthic disorders", "Mycobacterial infectious disorders", and "Protozoal infectious disorders", MedDRA HLT of "Listeria infections" and PT "Infection parasitic") will also be summarized.

Please refer to Section 8.5.5 of this SAP for handling of anaphylactic events, which are also on the list of risks of omalizumab.

The listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and will be based on the SS-PRERAND-S1 population.

8.3. Deaths and SAEs

SAEs will be listed and summarized in the same manner described in Section 8.2.

Any deaths occurring during the study will be listed separately with details to include time and cause of death.

8.4. Clinical Laboratory Evaluation

Clinical laboratory results will be measured at Screening and every three months until the end of Stage 1 (or Stage 1 OLE for participants who moved to Stage 1 OLE) and will include CBC with differential, complete metabolic panel, and urinalysis. Results will be converted to standardized units where possible.

For numeric laboratory results, descriptive statistics at each visit and the change from BLS1 to each follow-up visit, maximum post-BLS1, minimum post-BLS1 will be presented for each treatment arm and overall. Results will also be plotted to show patterns over time. Quantile plots with treatment arm medians as well as 25^{th} and 75^{th} percentiles plotted over time will be created.

For categorical laboratory results as well as clinically significant changes in numeric laboratory results relative to BLS1, the number and percentage of participants in each category at each visit will be presented for each treatment arm and overall. Shift tables will also be produced for all categorical laboratory results by creating cross-tabulations of results at BLS1 with each follow-up visit during Stage 1 and Stage 1 OLE. Post-BLS1 clinical laboratory results from an initial partial stage during Stage 1 or Stage 1 OLE that were taken prior to a restart will not be included in summaries.

A data listing for all clinical laboratory results will be provided for the SS-PRERAND-S1 population. The listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm

(if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date), Lab Category, Lab parameter, collection time, and will be based on the SS-PRERAND-S1 population.

A separate Lab Abnormality listing will be provided. This listing will replicate the content of the aforenoted clinical lab listing but will include only labs with abnormal values.

8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.5.1. Vital Signs

Vital sign measurements (including temperature, pulse rate, respiratory rate, systolic blood pressure, and diastolic blood pressure), height, and weight will be collected at each visit during Stage 1 and Stage 1 OLE. BMI will be calculated as weight[kg]/(height[m]^2).

Vital sign measurements and weight collected at each visit during Stage 1 and Stage 1 OLE will be summarized descriptively by Stage 1 treatment arm. Height and BMI will be summarized at Screening only.

The change from BLS1 to the end of Stage 1 (i.e., Week 16 in Stage 1) in vital sign measurements and weight will be summarized using descriptive statistics of median, first and third quartiles, and the number of participants. Summaries will be presented by Stage 1 treatment arm and overall for the PSS-S1 population.

The change from BLS1 to the end of Stage 1 OLE (i.e., Week 24 in Stage 1 OLE) and the change from Week 0 of Stage 1 OLE to the end of Stage 1 OLE in vital sign measurements and weight will be summarized using descriptive statistics of median, first and third quartiles, and the number of participants. Summaries will be presented by Stage 1 treatment arm and overall for the PSS-S1OLE population.

A data listing for vital sign measurements, height, and weight will be provided. Data will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and include an indicator for the SS-OFC-S1 and/or SS-OFC-S1OLE populations.

Post-BLS1 vital sign measurements from an initial partial stage during Stage 1 or Stage 1 OLE that were taken prior to a restart will not be included in summaries.

8.5.2. Physical Examinations

A complete physical examination will be performed at Screening, at each Screening DBPCFC Visit, at each DBPCFC Visit at the end of Stage 1, and at each DBPCFC Visit at the end of Stage 1 OLE.

Physical examination results of normal, abnormal, and not done will be summarized as frequencies and percentages by body system and visit for all participants. Shift tables will be produced by creating cross-tabulations of normal and abnormal results at BLS1 with each of the

DBPCFC Visits at the end of Stage 1 for the PSS-S1 population and BLS1 with each of the DBPCFC Visits at the end of Stage 1 OLE for the PSS-S1OLE population.

A data listing for physical examination results will be provided for the SS-PRERAND-S1 population with an indication of inclusion in the SS-S1OLE population and sorted by age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, participant ID, Stage, Restart Period, body system, and time of assessment. The clinical significance of any abnormal event will be noted in the listing.

Post-BLS1 physical examination results from an initial partial stage during Stage 1 or Stage 1 OLE that were taken prior to a restart as well as physical examination results that were taken upon restarting Stage 1 or Stage 1 OLE will not be included in summaries.

8.5.3. Events Associated with Accidental Exposure to Food Allergens

Accidental exposure to food allergens will be summarized by Stage 1 treatment group, using the PSS-PRERAND-S1, PSS-S1, and PSS-S1OLE populations separately to report the number of accidental exposures, the number of accidental exposures with vs without associated symptoms/AEs, and the number and type of symptoms/AEs associated with accidental exposure. Events will be included in this summary whether or not it was recorded as an AE.

The supporting listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of event (e.g., Stage, Restart Period, AE Start Date).

8.5.4. Dose-Limiting Symptoms During Oral Food Challenges

All dose-limiting symptoms that occur during a blinded OFC will be summarized as frequencies and percentages by symptom severity and type of dosing symptom for the blinded OFCs during the Screening DBPCFC in the PSS-PRERAND-OFC-S1 population, during the Screening DBPCFC and DBPCFC at the end of Stage 1 in the PSS-OFC-S1 population, and during the Screening DBPCFC, DBPCFC at the end of Stage 1, and DBPCFC at the end of Stage 1OLE in the PSS-S1OLE population.

Additionally, a data listing will be provided for all dose-limiting symptoms that occur during blinded OFCs. It will include All dose-limiting symptoms that occur during blinded OFCs in the Screening DBPCFC, the DBPCFC at the end of Stage 1, and the DBPCFC at the end of Stage 1 OLE and will be based on the SS-PRERAND-OFC-S1 population.

The listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and include an indicator for the SS-OFC-S1 and/or SS-OFC-S1OLE populations.

8.5.5. Anaphylaxis

All events of anaphylaxis that meet Sampson's criteria (see protocol) that do not occur during blinded OFCs will be summarized as frequencies and percentages by event type and AE grade in the PSS-S1 and PSS-S1OLE populations. A data listing for all events of anaphylaxis that meet Sampson's criteria (see protocol) that do not occur during blinded OFCs will be provided for the PSS-S1 sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., Stage, Restart Period, AE Start Date).

All events of anaphylaxis that meet Sampson's criteria (see protocol) that occur during blinded OFCs will be summarized by dosing symptom severity as frequencies and percentage of participants having at least one event in the following categories:

- Events of anaphylaxis that occur during blinded OFCs in the DBPCFC at the end of Stage 1 in the PSS-OFC-S1 population.
- Events of anaphylaxis that occur during blinded OFCs in the DPBCFC at the end of Stage 1, or DBPCFC at the end of Stage 1 OLE in the PSS-S1OLE population.

Similar tables will summarize all events of anaphylaxis that occur during blinded OFCs that also meet adverse event criteria. In this case, each table will be summarized by frequencies and percentages by AE grade. Additional tables will stratify AEs by those that occur prior to Protocol V2.0 and those that occur on or after Protocol V2.0.

Additionally, a data listing will also be provided for all events of anaphylaxis that meet Sampson's criteria that occur during the double-blind placebo-controlled OFC during Stage 1 and during Stage 1 OLE. The listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment, and time of assessment (e.g., Stage, Restart Period, AE Start Date) and will be based on the SS-OFC-S1 population.

9. PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION

9.1. Pharmacokinetic Methods

A data listing for omalizumab trough concentration, total IgE, and total free IgE will be provided for the FA-S1 population with an indication for inclusion in the FA-S1OLE population and sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm, participant ID, time of assessment (e.g., Stage, Restart Period, AE Start Date) and type of assessment (omalizumab trough concentration, total IgE, and total free IgE).

9.1.1. Pharmacokinetic Exploratory Endpoint 5-1 – 5-2

Endpoint: Omalizumab trough concentration will be measured at the first DBPCFC visit at the end of Stage 1 (Week 16) and the first DBPCFC visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE).

Analysis: Omalizumab trough concentration measured in Stage 1 will be summarized descriptively as continuous variables in the PFA-S1 and in the PFA-S1OLE population separately. Each summary will only include participants who received any injection (including a partial single dose) of omalizumab or placebo for omalizumab in Stage 1 and will be grouped by the omalizumab dosing frequency that was received in Stage 1. If any participant randomized to placebo for omalizumab receives one injection of omalizumab, a footnote will be included to indicate the participant. If more than one participant randomized to placebo for omalizumab receives any injection (including a partial single dose) of omalizumab, the PSS-S1 population will be used in place of the PFA-S1 population. As sensitivity analyses, similar summaries will be prepared excluding the participants that restarted Stage 1.

A similar summary will be prepared for PFA-S1 participants who restarted a stage due to COVID-19 summarizing omalizumab trough concentration before and after the hold for COVID-19.

Omalizumab trough concentration measured in Stage 1 OLE will be summarized in a similar manner as those for Stage 1 but will only include participants who received open label omalizumab in Stage 1 OLE and will be grouped by Stage 1 treatment arm and the omalizumab dosing frequency that was received in Stage 1 OLE.

9.1.2. Pharmacodynamic Exploratory Endpoint 6-1, 6-2, 7-1, and 7-2

Endpoint: PD biomarkers include the following:

1. Total IgE
2. Total free IgE

These PD biomarkers will be measured at the following times:

- Baseline (prior to the first Screening DBPCFC Visit, BLS1);
- First DBPCFC visit at the end of Stage 1; and
- First DBPCFC visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE).

Analysis: Each log-transformed PD biomarker measured during Stage 1 will be modeled using a linear (or nonlinear, if appropriate) mixed model (similar to Section 7.5.3) that will include a random intercept and fixed effects for treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1, time of measurement (BLS1 or first DBPCFC visit at the end of Stage 1), and an interaction term between treatment arm and time of measurement. The model will be used to estimate the following:

- The geometric mean ratio of the PD biomarker over time in each treatment arm.
- The geometric mean ratio of the geometric mean ratio in the PD biomarker over time between treatment arms.

PD biomarker will be summarized descriptively as continuous measures for the PFA-S1 population for Stage 1 and will include BLS1, the first DBPCFC visit at the end of Stage 1, and the change in PD biomarkers from BLS1 to the first DBPCFC visit at the end of Stage 1. Summaries will be provided by age at randomization (<18 years or ≥18 years) and treatment arm. As sensitivity analyses, similar summaries will be prepared excluding the participants that restarted Stage 1 due to COVID-19 and excluding the participants that restarted Stage 1 due to COVID-19 or for protocol-defined reasons.

A similar summary will be prepared for PFA-S1 participants who restarted a stage due to COVID-19 summarizing total free IgE before and after the hold for COVID-19.

PD biomarker will be summarized descriptively as continuous variables in the PFA-S1OLE population for Stage 1 OLE will include BLS1, the first DBPCFC visit at the end of Stage 1 OLE, and the change in PD biomarkers from BLS1 to the first DBPCFC visit at the end of Stage 1 OLE . Summaries will be provided by age at randomization (<18 years or ≥18 years) and Stage 1 treatment arm. If the sample size for any subgroup (defined by age at randomization and Stage 1 treatment arm) is <3 participants, it will not be summarized. A separate summary will be provided for all PFA-S1OLE participants, PFA-S1OLE participants who did not restart Stage 1 OLE due to COVID-19, PFA-S1OLE participants who restarted Stage 1 OLE due to COVID-19, PFA-S1OLE participants who did not restart Stage 1 OLE due to COVID-19 or other protocol-defined reasons, and PFA-S1OLE participants who restarted Stage 1 OLE due to COVID-19 or other protocol-defined reasons.

10. OTHER ANALYSES

10.1. Use of Concomitant (Prior and On-Study) Medication

Medications will be coded according to the latest version of the WHO Drug Dictionary. Medications reported on the CRF will be categorized for analysis as prior to Screening, during Screening, during Stage 1, or during Stage 1 OLE by comparing the medication start and stop dates with the date of Screening, date of first injection in Stage 1, and date of first injection in Stage 1 OLE.

Medications will be categorized in these non-mutually exclusive categories as follows:

Screening: Any medication with start dates and stop dates that overlap the screening period will be flagged as occurring in Screening. If a medication starts and stops on the day of Screening, it will be considered a Screening medication.

Stage 1: Any medication having a start and stop dates overlapping the Stage 1 period will be flagged as occurring in Stage 1. If a medication start date and stop date occur on the same day as the first injection of omalizumab or placebo for omalizumab in Stage 1, it will be considered a Stage 1 medication.

Stage 1 OLE: Any medication having start and stop dates that overlap the OLE period will be flagged as occurring in Stage 1 OLE. If a medication start date and stop date occur on the same day as the

first injection of open label omalizumab in Stage 1 OLE, it will be considered a Stage 1 OLE medication.

Partial and completely missing dates will be imputed for the purposes of classifying concomitant medications as follows:

- Partial dates will be imputed following the same algorithm as above for TEAEs.
- For a missing start date (i.e., day, month, and year are missing), the start date will be set to the date of Screening unless the stop date is prior the date of Screening, in which case the start date will be set to the stop date.
- For a missing stop date (i.e., day, month, and year are missing), the medication will be treated as ongoing.

The number and percentage of participants receiving prior (Screening) or on-study (post-randomization) medication will be presented overall and by medication class. When reporting the number of participants receiving the medication, a participant will only be counted once if they ever received the medication within the medication class during the Study Stage. Percentages will be based on the number of participants in the PSS-S1 population for Stage 1 and the PSS-S1OLE population for Stage 1 OLE.

A data listing will be provided for medications, taken during Screening, Stage 1, and Stage 1 OLE in the SS-PRERAND-S1 with an indication for the participants in the SS-S1OLE population.

10.2. Epinephrine Use

Epinephrine Use Not Occurring During Blinded OFC

All events where at least one dose of epinephrine was administered that do not occur during blinded OFCs will be summarized as frequencies and percentages by event type in the PSS-S1 and PSS-S1OLE populations. Additional characteristics of each event, such as when the event occurred (e.g., IDE, DBPCFC) will also be summarized.
A data listing for all events where at least one dose of epinephrine was administered that do not occur during blinded OFCs will be provided for the SS-PRERAND-S1 population with an indication for the SS-S1 or SS-S1OLE populations and sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, and time of assessment (e.g., visit, time, and/or event).

Epinephrine Use Occurring During Blinded OFC

All occurrences where at least one dose of epinephrine was administered during blinded OFCs will be summarized by dosing symptom severity as frequencies and percentage of participants having at least one event in the following categories:

- Events where at least one dose of epinephrine administered in a blinded OFC during the Screening DBPCFC in the PSS-PRERAND-OFC-S1 population.

- Events where at least one dose of epinephrine administered in a blinded OFC during the Screening DBPCFC or DBPCFC at the end of Stage 1 in the PSS-OFC-S1 population.
- Events where at least one dose of epinephrine administered in a blinded OFC during the Screening DBPCFC, DBPCFC at the end of Stage 1, or DBPCFC at the end of Stage 1 OLE in the PSS-S1OLE population.

Similar tables will summarize all events where at least one dose of epinephrine was administered during blinded OFCs that also meet adverse event criteria. In this case, each table will be summarized by frequencies and percentages by AE grade. Additional tables will stratify AEs by those that occur prior to Protocol V2.0 and those that occur on or after Protocol V2.0.

Additionally, a data listing will also be provided for all events where at least one dose of epinephrine was administered during blinded OFCs and will be based on the SS-PRERAND-S1 population. The listing will include all events where at least one dose of epinephrine was administered during a blinded OFC in Screening, Stage 1, or Stage 1 OLE:

The listing will be sorted in order of age at randomization (<18 years or ≥18 years), Stage 1 treatment arm (if applicable), participant ID, Stage, Restart Period, and time of assessment (e.g., visit, time, and/or event) and include an indication of inclusion in the SS-OFC-S1 and/or SS-OFC-S1OLE populations.

11. INTERIM ANALYSES AND DATA MONITORING

11.1. Safety Monitoring

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT SACCC compiling new and accumulating information on AEs, SAEs, AESIs, and pregnancies recorded by the CRUs on appropriate eCRFs.

The NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) will review safety data twice per year. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs, SAEs and AESIs that is created by the DAIT SACCC.

In addition to the pre-scheduled data reviews and planned safety monitoring, the NIAID Allergy and Asthma DSMB may be called upon for ad hoc reviews when an event occurs that is of sufficient concern to the DAIT/NIAID Medical Monitor and/or Protocol Chair or Co-Chair to warrant a DSMB review. The DSMB will be notified within 24-48 hours by the DAIT/NIAID Medical Monitor and will promptly review any event that potentially impacts safety at the request of the Protocol Chair or Co-Chair or DAIT/NIAID Medical Monitor or any occurrence that meets the definition of the study stopping

rules defined in the protocol. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

The DSMB will also review each omalizumab-associated anaphylactic reaction (i.e., an AESI) as identified by the PIs to confirm that the event: a) satisfies the criteria for anaphylactic reaction, and b) is associated with omalizumab.

All AEs as well as all pregnancies and use of epinephrine for both life-threatening and non-life threatening reactions will be included in the IND annual report submitted to the FDA by the Sponsor, DAIT/NIAID.

11.2. Planned Interim Analysis for Efficacy

An interim analysis for efficacy will be conducted on all pediatric participants randomized into Stage 1 by 08JUL2022 (N=165). The independent DSMB will be tasked with reviewing interim analysis results and communicating, with their recommendation, as to whether the interim analysis was considered to be successful for efficacy according to criteria described in Section 7.2. Efficacy would be declared at the interim only if the p-value for the peanut at interim is less than 0.0001 and the p-values for all secondary foods (cashew, milk, and egg) are less than <0.005.

Along with the analyses based on Fisher's exact test described in sections 7.3.2 (primary) and 7.4.1 (key secondary), supportive analyses based on exact logistic regression (see supplementary analysis #1 in Section 7.3.3.) will also be provided along with unblinded safety results (presented by treatment group) from the interim analysis population. Based on provided material, the DSMB will provide DAIT with a recommendation on study continuation.

Additional details for operating agreements along with roles and responsibilities for communication and expectations for data summaries will be documented separately.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Not applicable at this time.

13. REFERENCES

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2. Brannath W, Bretz F, Maurer W, Sarkar S. Trimmed weighted Simes' test for two one-sided hypotheses with arbitrarily correlated test statistics. Biometrical journal Biometrische Zeitschrift 2009;51:885-98.
3. O'Kelly M, Ratitch B. Clinical Trials with Missing Data: A Guide for Practitioners. First ed. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2014.
4. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002:1-190.

14. APPENDICES

14.1. List of Endpoints

Stage	Endpoint	Endpoint #
Stage 1	Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1	Primary Endpoint
Stage 1	Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Key Secondary Endpoint #1
Stage 1	Consumption of a single dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Key Secondary Endpoint #2
Stage 1	Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Key Secondary Endpoint #3
Stage 1	Consumption of a single dose of ≥600 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-1
Stage 1	Consumption of a single dose of ≥600 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-2
Stage 1	Consumption of a single dose of ≥600 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-3
Stage 1	Consumption of a single dose of ≥600 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-4
Stage 1	Consumption of a single dose of ≥600 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-5
Stage 1	Consumption of a single dose of ≥600 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-6
Stage 1	Consumption of a single dose of ≥600 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-7
Stage 1	Consumption of a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-8
Stage 1	Consumption of a single dose of ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-9
Stage 1	Consumption of a single dose of ≥1000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-10
Stage 1	Consumption of a single dose of ≥1000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-11
Stage 1	Consumption of a single dose of ≥1000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-12
Stage 1	Consumption of a single dose of ≥1000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-13
Stage 1	Consumption of a single dose of ≥1000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-14
Stage 1	Consumption of ≥1 dose of 2000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-15
Stage 1	Consumption of ≥1 dose of 2000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-16
Stage 1	Consumption of ≥1 dose of 2000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-17
Stage 1	Consumption of ≥1 dose of 2000 mg of wheat protein without dose-limiting	Secondary Endpoint #5-18

Stage	Endpoint	Endpoint #
	symptoms during the DBPCFC at the end of Stage 1.	
Stage 1	Consumption of ≥1 dose of 2000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-19
Stage 1	Consumption of ≥1 dose of 2000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-20
Stage 1	Consumption of ≥1 dose of 2000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-21
Stage 1	Consumption of ≥1 dose of 2000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-22
Stage 1	Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-23
Stage 1	Consumption of 2 doses of 2000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-24
Stage 1	Consumption of 2 doses of 2000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-25
Stage 1	Consumption of 2 doses of 2000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-26
Stage 1	Consumption of 2 doses of 2000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-27
Stage 1	Consumption of 2 doses of 2000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-28
Stage 1	Consumption of 2 doses of 2000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-29
Stage 1	Consumption of 2 doses of 2000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-30
Stage 1	Consumption of 2 doses of 2000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-31
Stage 1	Consumption of 2 doses of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #5-32
Stage 1	Number of foods consumed at a single dose of ≥600 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #6-1
Stage 1	Number of foods consumed at a single dose of ≥1000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #6-2
Stage 1	Number of foods consumed at ≥1 dose of 2000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #6-3
Stage 1	Number of foods consumed at 2 doses of 2000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.	Secondary Endpoint #6-4
Stage 1 OLE	Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-1
Stage 1 OLE	Consumption of a single dose of ≥600 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-2
Stage 1 OLE	Consumption of a single dose of ≥600 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-3
Stage 1 OLE	Consumption of a single dose of ≥600 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-4
Stage 1 OLE	Consumption of a single dose of ≥600 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-5
Stage 1 OLE	Consumption of a single dose of ≥600 mg of hazelnut protein without dose-	Exploratory Endpoint #2-6

Stage	Endpoint	Endpoint #
	limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	
Stage 1 OLE	Consumption of a single dose of ≥600 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-7
Stage 1 OLE	Consumption of a single dose of ≥600 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-8
Stage 1 OLE	Consumption of a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-9
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-10
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-11
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-12
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-13
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-14
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-15
Stage 1 OLE	Consumption of a single dose of ≥1000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-16
Stage 1 OLE	Consumption of a single dose of ≥1000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-17
Stage 1 OLE	Consumption of a single dose of ≥1000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-18
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-19
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-20
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-21
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-22
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-23
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-24
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-25
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-26
Stage 1 OLE	Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-27
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-28
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-29
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-30
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-31

Stage	Endpoint	Endpoint #
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-32
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-33
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-34
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-35
Stage 1 OLE	Consumption of ≥2 doses of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-36
Stage 1 OLE	Consumption of 3 doses of 2000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-37
Stage 1 OLE	Consumption of 3 doses of 2000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-38
Stage 1 OLE	Consumption of 3 doses of 2000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-39
Stage 1 OLE	Consumption of 3 doses of 2000 mg of wheat protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-40
Stage 1 OLE	Consumption of 3 doses of 2000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-41
Stage 1 OLE	Consumption of 3 doses of 2000 mg of hazelnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-42
Stage 1 OLE	Consumption of 3 doses of 2000 mg of walnut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-43
Stage 1 OLE	Consumption of 3 doses of 2000 mg protein of at least two foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-44
Stage 1 OLE	Consumption of 3 doses of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #2-45
Stage 1 OLE	Number of foods consumed at a single dose of ≥600 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #3-1
Stage 1 OLE	Number of foods consumed at a single dose of ≥1000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #3-2
Stage 1 OLE	Number of foods consumed at ≥1 dose of 2000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #3-3
Stage 1 OLE	Number of foods consumed at ≥2 doses of 2000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #3-4
Stage 1 OLE	Number of foods consumed at 3 doses of 2000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.	Exploratory Endpoint #3-5
Stage 1	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC visit at the end of Stage 1	Exploratory Endpoint #4-1
Stage 1 OLE	Change in quality of life between Week 0 in Stage 1 and the beginning of Stage 1 OLE	Exploratory Endpoint #4-2
Stage 1 OLE	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC visit at the end of Stage 1 OLE	Exploratory Endpoint #4-3
Stage 1 OLE	Change in quality of life between Week 0 in Stage 1 and the last DBPCFC visit at the end of Stage 1 OLE	Exploratory Endpoint #4-4
Stage 1	Omalizumab trough concentration measured at the first DBPCFC visit at the end of Stage 1	Exploratory Endpoint #5-1
Stage 1 OLE	Omalizumab trough concentration measured at the first DBPCFC visit at the end of Stage 1 OLE	Exploratory Endpoint #5-2
Stage 1	Total IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #6-1

Stage	Endpoint	Endpoint #
Stage 1 OLE	Total IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #6-2
Stage 1	Total free IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #7-1
Stage 1 OLE	Total free IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #7-2
Stage 1	Peanut IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-1
Stage 1	Milk IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-2
Stage 1	Egg IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-3
Stage 1	Wheat IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-4
Stage 1	Cashew IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-5
Stage 1	Hazelnut IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-6
Stage 1	Walnut IgE at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #8-7
Stage 1 OLE	Peanut IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-8
Stage 1 OLE	Milk IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-9
Stage 1 OLE	Egg IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-10
Stage 1 OLE	Wheat IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-11
Stage 1 OLE	Cashew IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-12
Stage 1 OLE	Hazelnut IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-13
Stage 1 OLE	Walnut IgE at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #8-14
Stage 1	Peanut IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-1
Stage 1	Milk IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-2
Stage 1	Egg IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-3
Stage 1	Wheat IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-4
Stage 1	Cashew IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-5
Stage 1	Hazelnut IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-6
Stage 1	Walnut IgG4 at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #9-7
Stage 1 OLE	Peanut IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-8
Stage 1 OLE	Milk IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-9
Stage 1 OLE	Egg IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-10
Stage 1 OLE	Wheat IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-11
Stage 1 OLE	Cashew IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-12
Stage 1 OLE	Hazelnut IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-13
Stage 1 OLE	Walnut IgG4 at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #9-14
Stage 1	Peanut IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-1
Stage 1	Milk IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-2
Stage 1	Egg IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-3
Stage 1	Wheat IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-4
Stage 1	Cashew IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-5
Stage 1	Hazelnut IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-6
Stage 1	Walnut IgA at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #10-7
Stage 1 OLE	Peanut IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-8
Stage 1 OLE	Milk IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-9
Stage 1 OLE	Egg IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-10
Stage 1 OLE	Wheat IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-11
Stage 1 OLE	Cashew IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-12
Stage 1 OLE	Hazelnut IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-13
Stage 1 OLE	Walnut IgA at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #10-14
Stage 1	Peanut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-1
Stage 1	Milk IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-2
Stage 1	Egg IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-3
Stage 1	Wheat IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-4
Stage 1	Cashew IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-5

Stage	Endpoint	Endpoint #
Stage 1	Hazelnut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-6
Stage 1	Walnut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #11-7
Stage 1 OLE	Peanut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-8
Stage 1 OLE	Milk IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-9
Stage 1 OLE	Egg IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-10
Stage 1 OLE	Wheat IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-11
Stage 1 OLE	Cashew IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-12
Stage 1 OLE	Hazelnut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-13
Stage 1 OLE	Walnut IgG4/IgE ratio at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #11-14
Stage 1	Basophil activation test to peanut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-1
Stage 1	Basophil activation test to milk at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-2
Stage 1	Basophil activation test to egg at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-3
Stage 1	Basophil activation test to wheat at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-4
Stage 1	Basophil activation test to cashew at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-5
Stage 1	Basophil activation test to hazelnut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-6
Stage 1	Basophil activation test to walnut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #12-7
Stage 1 OLE	Basophil activation test to peanut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-8
Stage 1 OLE	Basophil activation test to milk at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-9
Stage 1 OLE	Basophil activation test to egg at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-10
Stage 1 OLE	Basophil activation test to wheat at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-11
Stage 1 OLE	Basophil activation test to cashew at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-12
Stage 1 OLE	Basophil activation test to hazelnut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-13
Stage 1 OLE	Basophil activation test to walnut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #12-14
Stage 1	Skin prick test to peanut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-1
Stage 1	Skin prick test to milk at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-2
Stage 1	Skin prick test to egg at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-3
Stage 1	Skin prick test to wheat at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-4
Stage 1	Skin prick test to cashew at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-5
Stage 1	Skin prick test to hazelnut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-6
Stage 1	Skin prick test to walnut at the first DBPCFC at the end of Stage 1	Exploratory Endpoint #13-7
Stage 1 OLE	Skin prick test to peanut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-8
Stage 1 OLE	Skin prick test to milk at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-9
Stage 1 OLE	Skin prick test to egg at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-10
Stage 1 OLE	Skin prick test to wheat at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-11
Stage 1 OLE	Skin prick test to cashew at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-12
Stage 1 OLE	Skin prick test to hazelnut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-13
Stage 1 OLE	Skin prick test to walnut at the first DBPCFC at the end of Stage 1 OLE	Exploratory Endpoint #13-14