# Statistical Analysis Plan

Protocol No. ADP101-MA-01, 02 September 2022, Amendment 4

A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults (The Harmony Study)


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**Abbreviations**

| Abbreviation | Description |
|---|---|
| ACT | Asthma Control Test |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AF | Adult Form |
| ANCOVA | Analysis of Covariance |
| AS | Allergy Suspected |
| ATC | Anatomical Therapeutic Chemical |
| BL | Baseline |
| BMI | Body Mass index |
| C-ACT | Childhood Asthma Control Test |
| CF | Child Form |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CoFAR | Consortium of Food Allergy Research |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMS | Clinical Trial Management System |
| CV | Coefficient of Variation |
| DBPCFC | Double-Blind Placebo Controlled Food Challenge |
| DISP | Dosing Instructions and Symptom Management Plan |
| DLS | Dose-Limiting Symptom(s) |
| E9 | Statistical Principles for Clinical Trials |
| EAI | Epinephrine Autoinjector |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EEsAI | Eosinophilic Esophagitis Activity Index |
| EoE | Eosinophilic Esophagitis |
| EOT | End of Treatment |
| EOS | End of Study |
| ET | Early Termination |

| Abbreviation | Description |
|---|---|
| FA | Food Allergy |
| FAAP | Food Allergy & Anaphylaxis Emergency Care Plan |
| FAQL-PB | Food Allergy Quality of Life–Parental Burden |
| FAQLQ | Food Allergy Quality of Life Questionnaire |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced Expiratory Volume in the First Second |
| FU | Follow-Up |
| GCP | Good Clinical Practice |
| GLMM | Generalized Linear Mixed Model |
| GPP | Good Pharmacoepidemiology Practice |
| HRQoL | Health-Related Quality of Life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ID | Identification |
| iDMC | Independent Data Monitoring Committee |
| IgE | Immunoglobulin E |
| IgG4 | Immunoglobulin G Subclass 4 |
| IP | Investigational Product |
| IQoL | Immunotherapy-related quality of life |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ITT | Intent-to-Treat |
| KM | Kaplan-Meier |
| LLOQ | Lower Limit of Quantification |
| mApp | Mobile Application |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MH | Medical History |
| Min | Minimum |
| MMRM | Mixed-Model Repeated Measures |

| Abbreviation | Description |
|---|---|
| MTD | Maximum Tolerated Dose |
| NA | Not Applicable |
| NAS | No Allergy Suspected |
| ND | Not Definitive |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NHLBI | National Heart, Lung and Blood Institute |
| NPE | No Prior Exposure |
| NRND | Non-reactive-not-done |
| NRP | Non-reactive-Passed |
| OIT | Oral Immunotherapy |
| OLE | Open-Label Extension |
| PBMC | Peripheral Blood Mononuclear Cell |
| PDNCP | Protocol Deviation and Non-Compliance Management Plan |
| PE | Physical Examination |
| PEESS | Pediatric Eosinophilic Esophagitis Symptom Score |
| PEF | Peak Flow Meter |
| PEFR | Peak Expiratory Flow Rate |
| PF | Parent Form |
| PI | Principal Investigator |
| PP | Per-Protocol |
| PRACTALL | Practical Allergy |
| PRO | Patient-Reported Outcome |
| PT | Preferred Term |
| Q1:Q3 | First and Third Quartiles |
| QC | Quality Control |
| QTc | Corrected QT Interval |
| RNQ | Reactive-Non-Qualifying |
| RQ | Reactive-Qualifying |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |

| Abbreviation | Description |
|---|---|
| SD | Standard Deviation |
| SE | Standard Error |
| SI | Standard International System of Units |
| sIgE | Specific Immunoglobulin E |
| sIgG4 | Specific Immunoglobulin G Subclass 4 |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SP | Subject Privacy |
| SPT | Skin-Prick Test |
| TEAE | Treatment-Emergent Adverse Event |
| TFL | Table, Figure and Listing |
| TSQM-9 | Treatment Satisfaction Questionnaire for Medication 9-Item |
| UNS | Unscheduled Visit |
| ULOQ | Upper Limit of Quantification |
| WHO | World Health Organization |

# 1. Introduction

This statistical analysis plan (SAP) is a comprehensive and detailed description of strategy and statistical techniques to be used for the analyses of trial data from clinical study protocol ADP101-MA-01 version Amendment 4 dated September 02, 2022 (A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults (The Harmony Study)). The SAP will be finalized prior to database lock to ensure the credibility of the study results by pre-specifying the statistical methods for analyses.

This plan may be revised during the study to accommodate protocol amendments and to adapt to revisions in the analysis approaches. Any changes made to the planned analyses described in this SAP after the database lock will be documented and detailed in the Clinical Study Report (CSR) for this study.

The statistical principles applied in the design and planned analyses of this study will be consistent with the International Conference on Harmonization (ICH) guidelines E9 (Statistical Principles for Clinical Trials) and E9(R1) (Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials).

# 2. Study Objectives

## 2.1. Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of ADP101 as assessed by an increased threshold for clinical reactivity to at least one Qualifying Food for which the eliciting dose was ≤ 100 mg at Screening

## 2.2. Secondary Objective

The secondary objective of this study is:

- To evaluate the efficacy of ADP101 as assessed by an increased threshold to one or more Qualifying Foods (for which the eliciting dose was ≤ 100 mg at Screening)

## 2.3. Safety Objective

The safety objective of this study is:

- To evaluate the safety and tolerability of ADP101 in subjects with food allergy (FA)

## 2.4. Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate whether Non-qualifying Reactive Foods (eliciting dose > 100 mg) respond to treatment with ADP101
- To evaluate the impact of treatment on changes in FA-associated biomarkers
- To evaluate the impact of ADP101 on patient-reported outcome (PRO) measures, including FA-related quality of life, risk of accidental exposure, quality-of-life questionnaires, and treatment satisfaction
- To evaluate the development of confirmed new FAs to Non-reactive Foods contained in ADP101
- To explore additional safety endpoints

# 3. Study Design

## 3.1. Overall Design

This is a Phase 1/2, randomized, double-blind, placebo-controlled study of the efficacy and safety of ADP101 in subjects who are allergic to 1 or more of the 15 food sources included in ADP101. Approximately 72 subjects will be enrolled, including at least 60 subjects aged ≥ 4 to < 18 years at study entry and approximately 12 adult subjects (≥ 18 to ≤ 55 years old). Approximately 20 US sites will enroll subjects for this study.

The study will consist of a screening period followed by a double-blind, placebo-controlled treatment period and follow-up period (only for subjects not continuing to the open-label extension [OLE]) (Figure 1). The treatment period will consist of both pre-maintenance (baseline and updosing) and maintenance portions.

**Screening Period:** After providing informed consent with or without assent, as applicable, subjects will be screened to determine study eligibility over multiple visits (up to 12 weeks); initially, each subject will be screened for each of the 15 food sources of ADP101 using the screening evaluation to determine double-blind, placebo-controlled food challenge (DBPCFC) testing as described in Figure 2 and Figure 3. Briefly, clinical FA history and skin-prick test (SPT) results will be obtained for each of the 15 food sources and used to identify foods to be evaluated during screening through DBPCFCs. Additional clinical history will be obtained from subjects on other allergens to understand the subject's broader allergic profile. During screening, subjects will undergo a Screening DBPCFC to a maximum challenge dose of 1000 mg for each potentially reactive food source. In order to qualify for randomization, each subject must have dose-limiting symptoms at or below the 100-mg level during the Screening DBPCFC to at least 1 and no more than 5 of the food sources contained in ADP101.

For each subject, each of the food sources contained within ADP101 will be divided into 2 categories as shown in Figure 3:

1. Reactive Food, defined as either a) Qualifying Food that elicits a reaction at ≤ 100 mg during the Screening DBPCFC, or b) Non-qualifying Food that elicits a reaction at > 100 mg but ≤ 1000 mg during the Screening DBPCFC
2. Non-reactive Food, defined as foods that either a) do not meet clinical history and/or biomarker threshold criteria (SPT ≤ 3 mm above negative control) to undergo a Screening DBPCFC, or b) meet criteria to undergo a Screening DBPCFC and are tolerated through the 1000-mg dose level at the Screening DBPCFC

Subjects who are found to meet the categorization of Reactive Food that include qualifying food sources (to at least 1 and no more than 5 foods) will satisfy screening criteria to be randomized as long as they meet all other eligibility criteria.

**Pre-Maintenance of the Treatment Period:** At baseline (of the treatment period), eligible subjects will be randomized in a 2:2:1:1 ratio to 1 of 4 arms, with 2 arms in each dosing regimen

(low or high), to receive daily oral doses of study drug (either ADP101 or matching placebo) in a blinded fashion as shown in Table 1. Subjects will be assigned to the low- or high-dose regimen but will be blinded to whether their regimen is the active or placebo study drug. Randomization will be stratified by age group (≥ 4 to < 18 years of age, and ≥ 18 to ≤ 55 years of age). Baseline treatment will consist of oral administration of a single dose of study drug at 5 mg (equivalent to 0.33 mg/food source) under direct medical supervision at the study site, and, if tolerated, will continue at 5 mg/day at home for 2 weeks. Subjects who are unable to tolerate up to 3 attempts to administer study drug at dose levels at or below 50 mg during the updosing portion of the treatment period will discontinue study drug and continue with study assessments. If a subject is unable to tolerate 5 mg after 3 tries, this will trigger randomization of another subject.

**Table 1 Treatment Groups**

| Treatment Group | Treatment | Regimen | Target Dose Level | Estimated Number of Subjects | Estimated Number of Subjects per Age Group Category (years) | |
|---|---|---|---|---|---|---|
| | | | | | ≥ 4 to < 18 | ≥ 18 to ≤ 55 |
| 1 | ADP101 | Low-dose | 1500 mg/day (100 mg per food source) | 24 | 20 | Approximately 4 |
| 2 | ADP101 | High-dose | 4500 mg/day (300 mg per food source) | 24 | 20 | Approximately 4 |
| 3 | Placebo | Low-dose | (Content volume-matched) | 12 | 10 | Approximately 2 |
| 4 | Placebo | High-dose | (Content volume-matched) | 12 | 10 | Approximately 2 |

Subjects who tolerate at least 50 mg/day will continue in the updosing portion of the study, and will return to the clinic every 2 weeks for updosing under direct medical supervision until the randomized target dose of 1500 mg/day (100 mg per food source; low-dose regimen) or 4500 mg/day (300 mg per food source; high-dose regimen) is achieved (Figure 1). If a subject fails 3 updosing attempts to any dose level above 50 mg/day, the site should contact the Study Medical Monitor for further guidance regarding additional updosing. Subjects who are unable to reach the randomized target dose will continue on the highest dose level they are able to reach, as long as the dose of study drug is at least 50 mg. Subjects may updose through Week 38, at which point the Week 38 dose will be maintained through the end of the study. Therefore, the duration of pre-maintenance (during the treatment period) is anticipated to be of variable length depending on how quickly subjects are able to reach their randomized target dose or maintenance dose.

**Maintenance of the Treatment Period:** Once the randomized target dose (or maintenance dose) is achieved, it will be maintained until Week 40. The maintenance portion of the treatment period may range from 2 to 22 weeks. Once a subject enters maintenance (e.g., no further updosing is planned), study visits will continue at every 2 weeks; however, on-site visits can be

spaced out to every 4 weeks and the other visits performed via tele-visit.. Vital signs and physical examination can be skipped for these visits. The Weeks 12, 20, 24, and 38 visits must be performed on-site.

**Exit Food Challenge/Week 40 Visit**: At the Week 40 visit, all subjects will undergo an Exit DBPCFC for all Reactive Foods determined during Screening. The Week 40 visit will be done over multiple visits (for up to 6 weeks, or extended to up to 8 weeks if a subject requires > 6 food challenges) to allow for adequate separation of individual DBPCFC procedures. The Exit DBPCFCs (Figure 4) will be performed in accordance with Practical Allergy (PRACTALL) guidelines (Sampson, 2012) and will require progression in an unaltered sequence, without repeating any dose. The Exit DBPCFCs will assess the same levels as done at study entry, as well as evaluating higher levels of up to 4000 mg of protein of each reactive food source (see Figure 4).

In order to obtain results before the Week 40 assessments begin, subjects will have an expanded study visit at Week 38. SPTs will be performed for all 15 foods. Foods that were determined to be a Non-reactive Food at Screening will be reevaluated to assess for development of a potential new FA during the treatment period. Each Non-reactive Food at Screening will be assessed for any new clinical symptoms resulting from the food source; SPT results will also determine which additional foods, if any, will get an Exit DBPCFC, per Figure 4. Only positive results on the DBPCFC will define a new FA developed during the treatment period.

Subjects will continue on study drug during the Exit DBPCFC period, but the daily study drug dose will be withheld on the day of the DBPCFC (± additional days per investigator judgment).

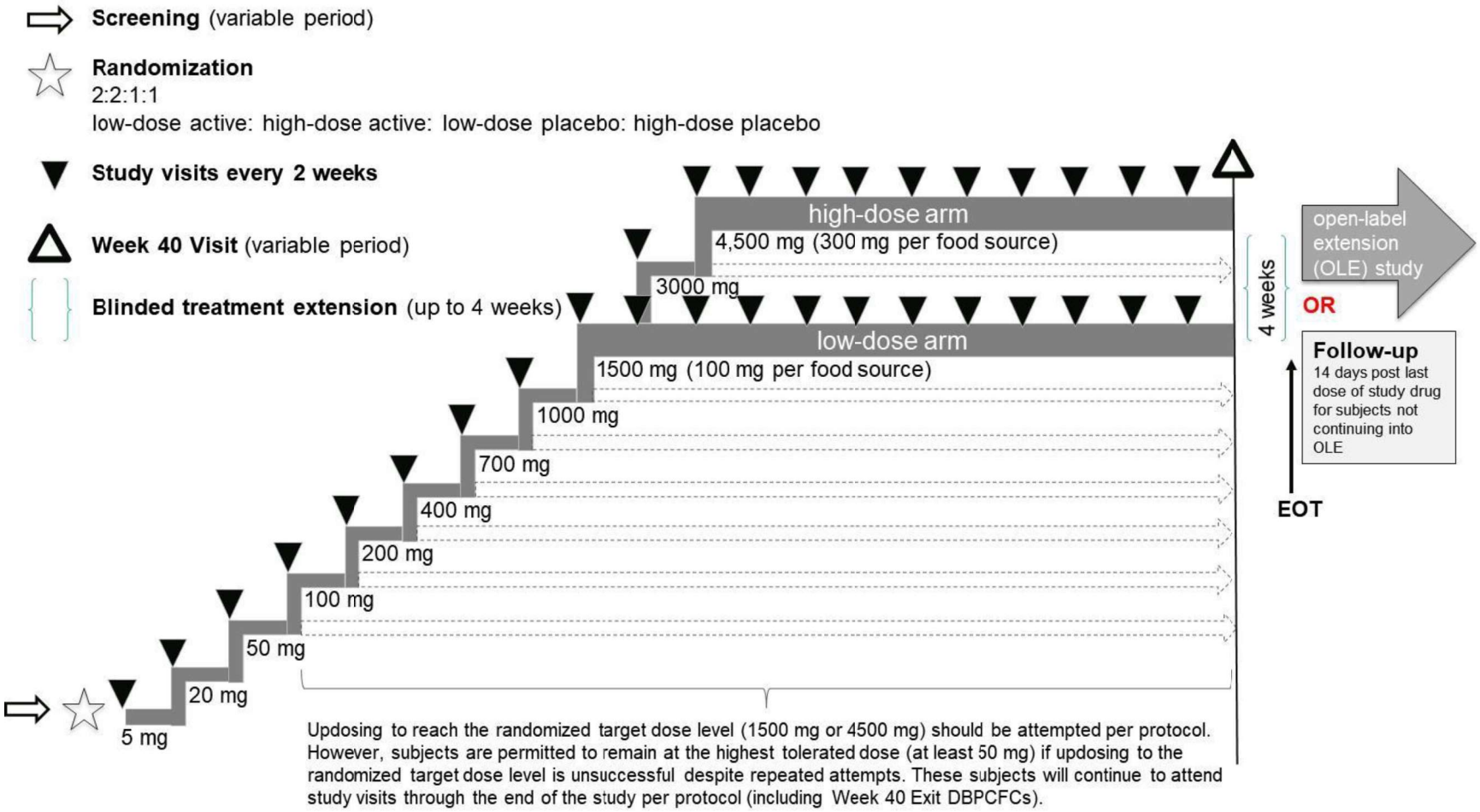
**End of Treatment:** After the final Exit DBPCFC, all subjects will continue to receive study drug at their maintenance dose for up to 4 weeks in a blinded treatment extension period, followed by the End of Treatment (EOT) visit, in order to maintain the blind during subject-level data cleaning. Thereafter, eligible subjects (taking either ADP101 or placebo) who complete the study (through EOT) will be unblinded in a rolling order and assessed for eligibility for the ADP101 open-label extension (OLE) study (under a separate protocol [ADP101-MA-02] and informed consent/assent).

**Follow-Up Period:** Subjects who are ineligible for or do not wish to continue to the OLE will receive instruction by the investigator about withdrawal from study drug and attend a follow-up visit 14 days from the EOT visit.

Throughout the study, subjects will undergo safety and efficacy assessments as specified in the Schedule of Activities (Appendix 1). Unscheduled visits can be conducted at any time during the study, as clinically indicated. Over the duration of the study, subjects should continue to avoid foods in their diet to which they are reactive (at any level).

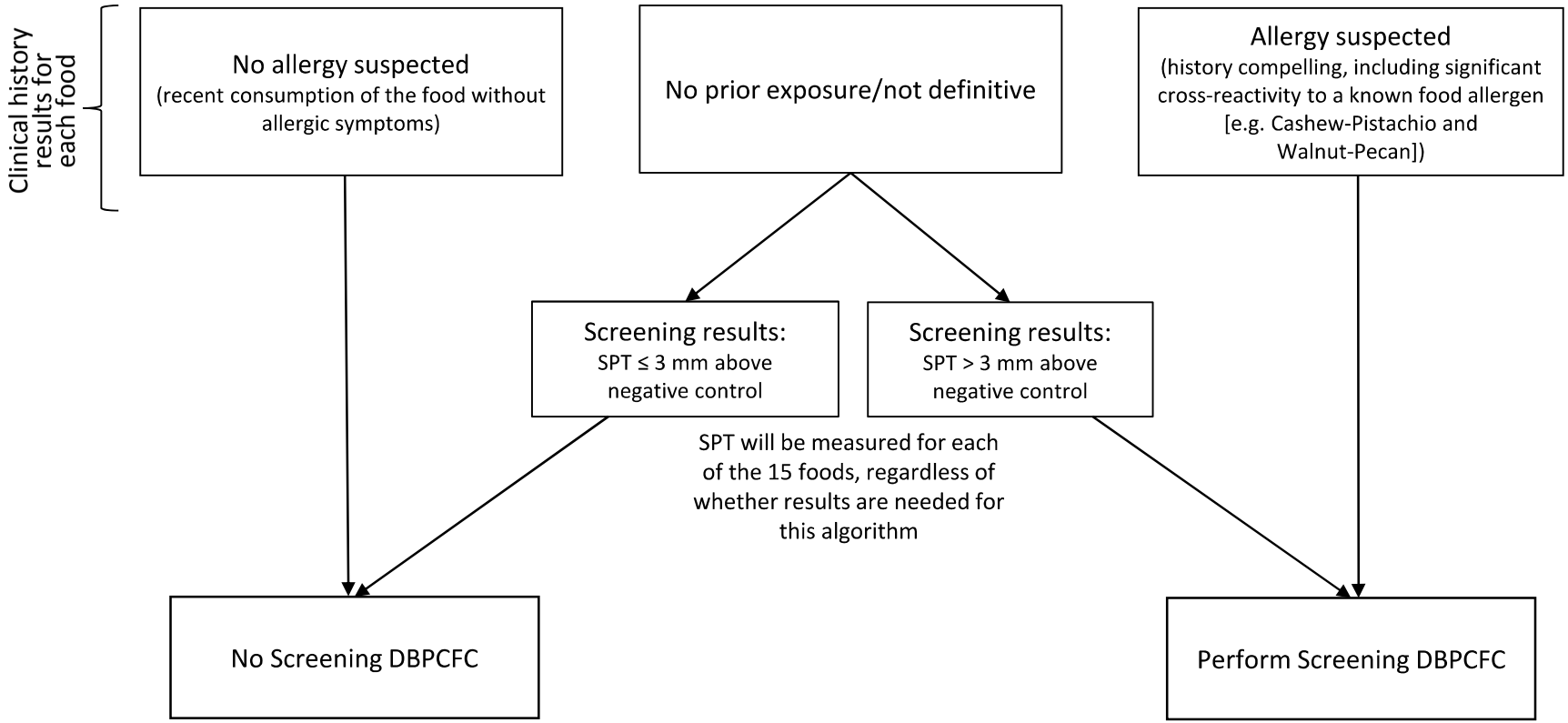
Details of study assessments and procedure conducted during the study are provided in the protocol Section 8 “STUDY ASSESSMENTS AND PROCEDURES.”

**Figure 1 Study Schema**



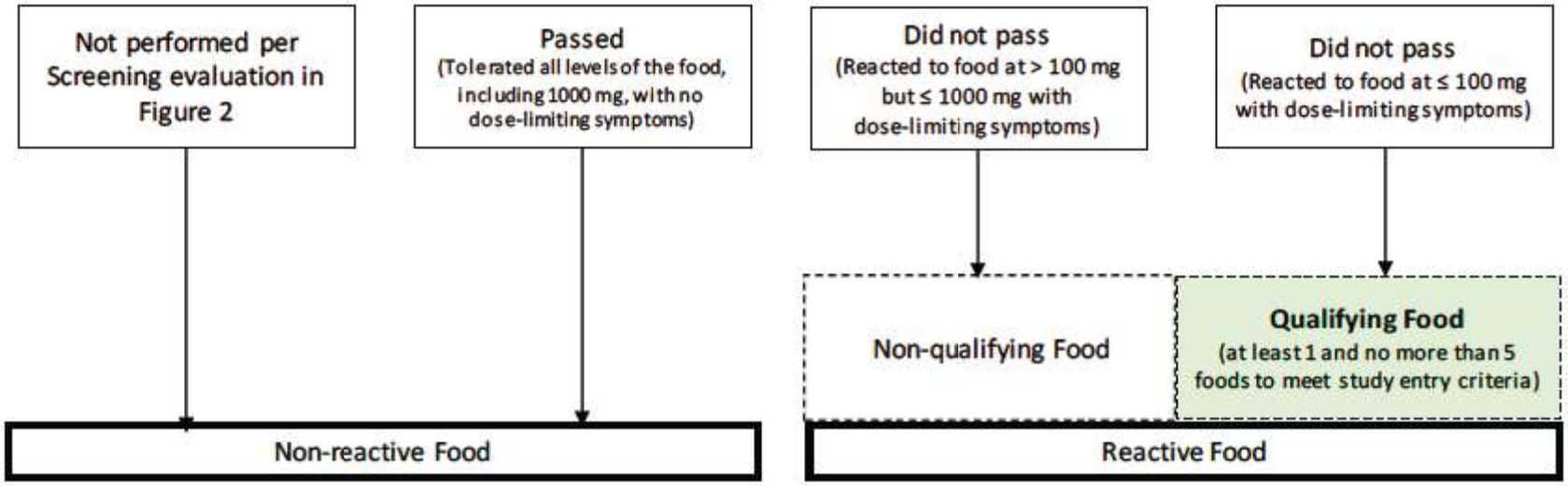

Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge; EOT = End of Treatment; OLE = open-label extension.

**Figure 2 Screening Evaluation to Determine Individual Food DBPCFC Testing**



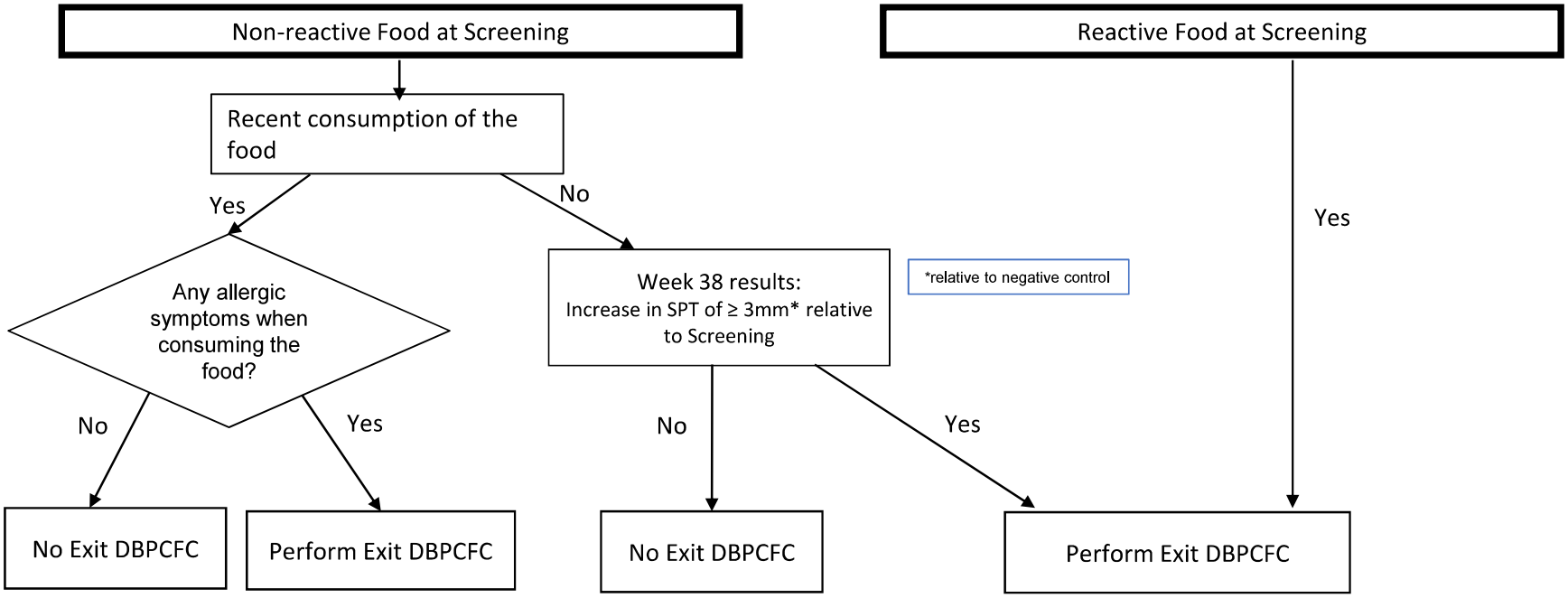

Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge; SPT = skin-prick test.

**Figure 3 Categorization of Individual Foods in ADP101 for Each Subject Based on Study Entry Criteria and Results of Screening DBPCFC**




Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge.

**Figure 4 Exit (Week 40 Visit) Evaluation to Determine Individual Food DBPCFC Testing**




Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge; SPT = skin-prick test.
Notes: *Formula: (Exit SPT – exit negative control) – (Screening SPT – screening negative control) ≥ 3mm.

### 3.2. Sample Size Determination

The total sample size required is 48 subjects (16:16:8:8) (high-dose ADP101: low-dose ADP101: high-dose placebo: low-dose placebo) for the study. Assuming a 20% pediatric subject dropout rate based on the dropout rate observed in prior oral immunotherapy (OIT) studies, a total of 60 pediatric subjects will be randomized 2:2:1:1 into the 4 arms. The planned randomization scheme is anticipated to enable completion through Week 40 for 16 subjects in each active dose regimen, and a total of 16 subjects taking placebo (8 per placebo dose regimen).

The adequacy of the sample size was confirmed by performing simulations for power calculations using the Fisher's exact test for each of 2 doses (vs. placebo) under alternative hypotheses. Assuming placebo response rates of 4% and active response rates of 40% and 58% in the low- and high-dose regimen treatment groups, respectively (based on (Vickery, 2018)), and an alpha of 5%, power was calculated using the Simes global test (Simes, 1986) with the Holm procedure (Holm, 1979) to reject at least 1 of the doses. Results showed approximately 90% power to detect a statistically significant ADP101 response in at least 1 of the doses with the given sample size.

Additionally, a total of approximately 12 adult subjects will be randomized to the 2 doses of ADP101 (approximately 4 subjects on each of the high- and low-dose regimens and 4 subjects on placebo), to provide an initial exploration of the safety and efficacy in this population, as well as the feasibility of enrolling adult subjects in subsequent studies with ADP101. Thus, a total of approximately 72 subjects will be enrolled in this study.

The sample size for the study is sufficient to test the superiority of ADP101 over placebo for pediatric subjects aged ≥ 4 to < 18 years who tolerate at least 600 mg on the Exit DBPCFC of a single qualifying food source within ADP101 without dose-limiting symptoms after 40 weeks of treatment (primary efficacy endpoint) with at least 1 of the 2 dosing regimens (low/1500 mg or high/4500 mg).

A claim of statistical significance will be not be made for the primary endpoint unless the superiority of ADP101 over placebo is demonstrated in at least 1 of the 2 doses (treatment groups).

### 3.3. Randomization

All subjects will be centrally randomized in a 2:2:1:1 ratio to 1 of 4 treatments, with 2 treatments in each dosing regimen (low or high), to receive daily oral doses of study drug (either ADP101 or matching placebo) in a blinded fashion using interactive response technology (IRT). The randomization schedule will be generated by an independent unblinded statistician from Syneos Health using SAS® software. The randomization schedule will be managed in the Suvoda IRT system. Randomization will be stratified by age group (≥ 4 to < 18 years of age and ≥ 18 to ≤ 55 years of age). Before the study is initiated, the access directions for the Suvoda IRT will be provided to each site. If a subject fails updosing after 3 consecutive attempts of study drug at 5

mg, an additional subject will be randomized to the study without impacting the overall 2:2:1:1 randomization ratio.

## 3.4. Blinding

This study is double-blinded. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining whether unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Alladapt prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, Alladapt must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Since subjects will have the option to rollover into the OLE study, this study will clean and lock the data at a per-subject level. Subject data will be unblinded on a rolling basis. For the final analysis specified in this SAP, the database for the whole study is locked when all subjects' data are locked. The subjects' randomized treatment assignments will be obtained from the Suvoda (IRT vendor) after obtaining proper authorization from Alladapt. These treatment assignments will then be incorporated into the analysis datasets, tables, listings, and figures.

# 4. Study Endpoints

## 4.1. Primary Endpoint

The primary endpoint of the study is:

- Proportion of subjects who tolerate the 600-mg level of a single Qualifying Food without dose-limiting symptoms at the Exit DBPCFC

## 4.2. Secondary Endpoints

The secondary endpoints of the study are:

- Proportion of subjects who tolerate the 1000-mg level of a single Qualifying Food without dose-limiting symptoms at the Exit DBPCFC
- Proportion of subjects with > 1 qualifying FA who tolerate the 600-mg level of each of 2 or more Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC
- Proportion of subjects with > 1 qualifying FA who tolerate the 1000-mg level of each of 2 or more Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC

## 4.3. Safety Endpoints

The safety endpoints of the study are:

- Incidence of adverse events (AEs)
- Incidence of serious adverse events (SAEs)

## 4.4. Exploratory Endpoints

The exploratory endpoints of the study are:

- Change from baseline in eliciting dose of each individual Reactive Food at the Exit DBPCFC
- Changes from baseline in biomarkers, including, but not limited to, specific immunoglobulin E (sIgE) and specific immunoglobulin G subclass 4 (sIgG4), of all foods contained in ADP101
- Change from baseline in SPT for all foods contained in ADP101
- Quality-of-life changes over time using the following:
  - Food Allergy Quality of Life Questionnaire (FAQLQ)
  - Accidental exposure questionnaire
  - Immunotherapy-related quality-of-life (IQoL) questionnaire
  - 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM 9)
  - Food Allergy Quality of Life–Parental Burden (FAQL-PB) questionnaire
- Proportion of subjects who develop confirmed new FAs to previously Non-reactive Foods at Screening as demonstrated by the Exit DBPCFC
- Incidence of AEs that lead to withdrawal from the study and/or discontinuation of study drug

- Incidence and shifts of clinically significant abnormalities in laboratory tests, vital signs, and spirometry forced expiratory volume in the first second (FEV1)/peak expiratory flow rate (PEFR)
- Frequency of allergic reaction AEs during treatment normalized for duration of treatment

### 4.5. Other Exploratory Endpoints

The following exploratory endpoints were not mentioned in the study protocol and will be analyzed:

- Maximum tolerated dose (MTD) for each qualifying reactive FA and for each non-qualifying reactive FA. The MTD is defined as the maximum single dose of a food source resulting in no dose-limiting symptoms as assessed by the investigator to have been tolerated during a DBPCFC
- Proportion of subjects with their MTDs at Exit DBPCFC greater than their MTDs at Screening DBPCFC for that food in each treatment group for the following food sources: peanut, tree nut, milk, soy, wheat, sesame, fin fish, shrimp, and egg
- Use of Epinephrine as a rescue medication for AEs
- Proportion of subjects with accidental exposure, including any accidental exposure, accidental exposure requiring treatment, and accidental exposure requiring hospitalization
- Maximum severity of allergy symptoms for each qualifying reactive FA and for each non-qualifying reactive FA at the screening and exit DBPCFCs
- Maintenance dose for study drug, which is defined as the study drug dose with which the subject is last treated before Exit DBPCFC or EOT (whichever occurs earlier) and tolerated for at least 2 weeks

# 5. Analysis Populations

The following analysis population will be used for the statistical analysis in this study.

## 5.1. Screened Population

The Screened Population is defined as all subjects who are screened, that is, subjects whose parents and/or themselves (adults) signed informed consent. Unless specified otherwise, this set will be used for specific data listings and summaries, for example, screening DBPCFC results for screened subjects.

## 5.2. Safety Population

The Safety Population is defined as all randomized subjects who receive at least 1 dose of study drug (ADP101 or placebo). Subjects will be analyzed according to treatment actually received. The Safety Population will be used for all analyses of safety endpoints.

## 5.3. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all randomized subjects. Subjects will be analyzed according to randomized treatment. The ITT Population will be used as the primary analysis set for all analyses of efficacy endpoints, subject disposition, demographics and baseline characteristics, and treatment exposure.

## 5.4. Per Protocol Population

The Per Protocol (PP) Population is defined as all subjects from the ITT Population without major protocol deviations that impact statistical analyses (e.g., eligibility criteria not met, poor compliance, nonpermitted medications, noncompletion of the Exit DBPCFCs) and who have Screening and Exit DBPCFCs (primary efficacy measurement). The PP Population will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria of the PP Population will be determined before database lock and treatment unblinding.

# 6. General Considerations for Statistical Analysis

## 6.1. General Methods

The following general guidelines will apply to all statistical analyses conducted for this study:

- SAS® version 9.4 or higher will be used.
- Unless otherwise specified, table summaries will be presented by pediatric subjects (≥ 4 to < 18 years old) and all subjects (pediatric and adult subjects combined), treatment group and overall. For the primary and secondary endpoints, the table summaries will be provided for the adult subjects (≥ 18 to ≤ 55 years old) as well. In general, for the purpose of data summaries, treatment group for the outputs would be (Low-Dose ADP101, High-Dose ADP101, Pooled ADP101 and Pooled Placebo)
- In general, continuous variables will be summarized using the descriptive statistics for the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). The min and max values will be presented to the same number of decimal places as the raw data. The means and medians will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data. If the raw data has 3 decimal places or more, 3 decimal places will be presented for mean, median, min and max, and SD. The use of other descriptive statistics will be noted where applicable.
- Categorical variables will be summarized using number of subjects or frequency (n) and percentages of subjects. All percentages will be presented with 1 decimal place. Percentages equal to 100% will be presented as 100%, and percentages will not be presented for zero counts. The categories whose counts are zero will be displayed for the sake of completeness. The percentages will be based on total number of subjects in the specified study analysis set under each treatment group (N), unless stated otherwise in the table shell.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings. Unless otherwise specified, the listings will be sorted by treatment group, subject number, and assessment date (and time) if applicable.
- All tests of treatment effect will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Any confidence intervals (CIs) of the statistical models will be rounded to 1 decimal place. All model estimates, such as least-squares (LS) means if applicable, will be rounded to 2 decimal places. Any calculated p-values will be rounded to 3 decimal places; p-values less than 0.001 will be presented as '$p < 0.001$' and p-values greater than 0.999 will be presented as '$p > 0.999$'.
- Multiple assessments at a given time point (planned, repeat, and unscheduled) will not be included in summary tables unless specified otherwise, but will be included in the listings. All assessments will be used in analysis of maximum changes or shift analyses.

## 6.2. Key Definitions

The following definitions and derivations will be used throughout the study. For the purpose of analysis, these definitions provide the operational definitions of key study concepts in terms of data points as they are collected in this study.

### 6.2.1. Maintenance Dose for Study Drug

The maintenance dose for study drug is defined as the study drug dose with which the subject is last treated before the Exit DBPCFC or EOT (whichever occurs earlier) and tolerated for at least 2 weeks.

### 6.2.2. Maximum Tolerated Dose (MTD) in DBPCFC

The MTD is specific to the food challenges. The MTD in DBPCFC is defined as the maximum single dose of a food source resulting in no dose-limiting symptoms and assessed by the investigator to have been tolerated (i.e., subject did not experience any dose-limiting symptoms). This will be determined for each food that is challenged via a DBPCFC. The MTD at the Screening DBPCFC will be used as the baseline amount of a food source tolerated.

Similarly, the eliciting dose (reactive dose) is defined as the dose given for each food source that induces the onset of dose-limiting symptoms at which the investigator stops the challenge.

### 6.2.3. Study/Treatment Period

The study period is the time from the date a subject or parent signed the informed consent/assent to the last day of follow-up. It includes the screening period, treatment period, and follow-up period (only for subjects who do not participate in the OLE study).

**Screening Period**

The screening period will be up to 12 weeks, including Screening DBPCFC(s) and other screening assessments. The first day of the screening period is the date of informed consent/assent. The last day of the screening period is the day before the date of first dose of study drug. If the subject is re-screened, the duration of the re-screen period must be within 12 weeks, even though some of the food challenges may have been conducted earlier.

**Treatment Period**

The treatment period will be up to 50 weeks, including 40 weeks of treatment plus up to 6 weeks for Exit Food Challenge/Week 40 (this period may be extended to up to 8 weeks if a subject requires > 6 food challenges) and up to 4 weeks of continued blinded study treatment through EOT. The treatment period will consist of pre-maintenance (including Baseline and updosing portions), maintenance, Exit Food Challenge/Week 40 Visit, and EOT as described in Section 3.1. Pre-maintenance, maintenance and Exit Food Challenge/Week 40 Visit durations will be variable per subject.

The start of the pre-maintenance period is marked by the date of Day 1 (Baseline). The start of the maintenance period is marked by the date of first dose of the sequence of maintenance doses administered closest to the first Exit Food Challenge/Week 40 Visit assessment. The Exit Food Challenge/Week 40 Visit period starts with the date of the first Week 40 Visit assessment and the end of this period is the last day of the last DBPCFC.

**Follow-Up Period**

Subjects who are ineligible for or do not wish to continue to the OLE study will receive instruction by the investigator about withdrawal from study drug and attend a Follow-Up Visit. The follow-up period will be 14 days from the EOT Visit. The beginning of the follow-up period is marked by the date of the EOT Visit + 1.

### 6.2.4. Baseline and Change from Baseline

Unless otherwise specified, the baseline value is defined as the last non-missing value prior to the first dose of study drug.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value, i.e., Post-baseline Assessment Value – Baseline Value.

### 6.2.5. Study Day

Day 1 is defined as the day of the first dose of study drug. Relative study days after Day 1 are calculated as (Assessment date – Date of Day 1 + 1). Relative study days prior to Day 1 are calculated as (Assessment date – Date of Day 1). The day prior to Day 1 is Day -1. There is no Study Day 0.

### 6.2.6. Treatment Exposure

#### 6.2.6.1. Exposure Duration

Subject exposure data are not collected on the study electronic case report form (eCRF). Rather they come from 2 external sources:

- Study drug accountability (in-clinic) data from Suvoda IRT system.
- Subject daily dosing diary data (non-clinic data) via mobile application (mApp) managed by AiCure. This data will be sent directly to Alladapt for exploratory analysis and are not planned to be included in the CSR of this study

The main calculation of exposure will be based on in-clinic dosing data and the dose level of the dispensed study drug from Suvoda IRT system.

**Exposure Duration: Overall Treatment Period**

The overall exposure duration (in days) is defined as [Last dose date of treatment – First dose date of treatment + 1].

A combination of the data from the EOT eCRF and the dose information from Suvoda IRT will be used to determine the date of last dose of treatment. For analysis purposes, the date of last study drug administration on the EOT eCRF will be used as the analysis date of last dose date.

**Exposure Duration: By Dose Level**

At each dose level within the treatment period, the exposure duration (in days) is defined as [Last Dose Date – First Dose Date + 1]. For any subject who has non-continuous dosing at the same dose level due to down dosing, the durations of the individual non-continuous intervals of such dosing are defined as [Last Dose Date of Interval – First Dose Date of Interval +1]. The exposure in days for such subjects at a given dose level would be the sum of the lengths of the individual non-continuous dosing intervals in days for all such non-continuous dosing.

**Exposure Duration: Pre-maintenance**

The exposure duration of pre-maintenance is anticipated to be of variable length depending on how quickly subjects are able to reach their randomized target dose or maintenance dose.

The exposure duration of pre-maintenance dosing (in days) is defined as [(The day prior to first dose of the sequence of maintenance doses administered closest to the first Exit Food Challenge/Week 40 Visit assessment) – (First dose date of treatment from Baseline Visit) + 1].

**Exposure Duration: Maintenance**

The exposure duration of the maintenance dosing is defined as [(Date of last maintenance dose before the Exit Food Challenge/Week 40) - (Date of first dose of the sequence of maintenance doses administered closest to the first Exit Food Challenge/Week 40 Visit assessment) + 1].

**Exposure Duration: Exit Food Challenge/Week 40**

The exposure duration of the Exit Food Challenge/Week 40 dosing (during the treatment period) is defined as [(Date of last dose during Exit Food Challenge/Week 40) - (Date of first dose during Exit Food Challenge/Week 40) + 1].

**Exposure Duration: EOT**

The exposure duration of the EOT dosing (during the treatment period) is defined as [(Date of last dose during the EOT) - (Date of first dose during the EOT) + 1]. The date of last dose will be the date of last study drug administration on the EOT eCRF.

#### 6.2.6.2. Unsuccessful Dose Increase

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

### 6.3. Missing Data

**Efficacy Endpoints**

Any methods for dealing with missing data where manipulation of the data is planned for each efficacy endpoint are covered in the relevant section of efficacy analysis below.

**Adverse Event Dates, Relationship and Severity**

Missing day will be imputed as the first day of month for all start dates, and as the last day of the month for all stop dates.

Missing month will be imputed as January for all start dates and as December for all stop dates.

The imputed start date will be compared to the informed consent form date (ICF) to ensure it makes sense and falls on or after the ICF date. If it falls before the ICF, then set the imputed start date to the ICF.

If the stop date is complete, and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

The imputed stop date will be compared to the last study date or death date and will be set to the last study date or death if the proposed imputed date is beyond the later of these dates.

Completely missing start dates for AEs will be imputed as the start date of treatment, if the end date is completely missing. Completely missing start dates for AEs will not be imputed, if the end date is completely available, as the position of the end date as either before or after the first dose date will be used to determine treatment-emergent adverse event (TEAE) status. No imputations will be done for subjects who did not receive study drug.

TEAEs will be considered treatment-related if relationship information is missing. Similarly, TEAEs will be considered severe if the severity information is missing.

**Concomitant Medication Dates**

Missing day will be imputed as the first day of month for all start dates, and as the last day of the month for all stop dates.

Missing month will be imputed as January for all start dates and as December for all stop dates.

The imputed start date will be compared to the ICF to ensure it makes sense and fall on or after the ICF date. If it falls before the ICF date, then set the imputed start date to the ICF.

If the stop date is complete, and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

The imputed stop date will be compared to the last study date or death date and will be set to the last study date or death if the proposed date is beyond the later of these dates.

Completely missing start dates for concomitant medications will be imputed as the start date of treatment, if the end date is completely missing. Completely missing start dates for concomitant medications will not be imputed, if the end date is completely available, as the position of the end date as either before or after the first dose date will be used to determine the status of

whether a medication is prior or concomitant. No imputations will be done for subjects who did not receive study drug.

**Medical/Allergy History Dates**

For partial start date in medical history and allergy history eCRF pages, impute as follows:

- Missing day is set to 1 if the same year and month as the informed consent date. Otherwise set it to 15
- Missing month is set to Jan if the same year as the informed consent date. Otherwise set it to July
- Missing month and day are set to Jan 1 if the same year as the informed consent date. Otherwise set it to July 1.

## 6.4. Visit Considerations

### 6.4.1. Visit Windows

All information will be listed, summarized, and analyzed according to the nominal visit time point, study period, or dose.

In the analysis, visit windows may be used as needed. The lower and upper bounds of a given visit window will be the halfway point between the given visit and prior analysis visit and halfway point (inclusive) between the given visit and next analysis visit. Unless otherwise specified, if a subject has more than one measurement included within a window, the measurement at the scheduled visit will be used; if there are no measurements at the scheduled visit, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the later assessment will be used.

### 6.4.2. Study/Treatment Period

The study consists of the following periods/portions: Screening Period, Pre-maintenance Period (Baseline and Updosing Portion), Maintenance Period, Exit Food Challenge/Week 40 Visit, EOT, and Follow-up Period. See Section 6.2.3 of this SAP for details.

### 6.4.3. Relationship between Analysis Visit and Study/Treatment Period

There is currently no direct readily identifiable information for study periods in the Suvoda IRT system. For the purposes of analysis, in order to generate data summaries by study period as described in this SAP, these periods will be derived as a "Visit Period" variable in the analysis datasets for the study by mapping to study visits that fall into each period.

The derivation of these periods is as follows:

- **Screening Period:** This will be up to 12 weeks from the day a subject or parent sign the informed consent/assent form to screen for the study. The visit, date and data corresponding to this period will be the screening visit, date, and data from the eCRF for each data domain. For occurrence datasets such as adverse events and concomitant

medications, a start date of informed consent date and an end date 1 day prior to the Day 1 Visit in Suvoda IRT system will be used to classify data into this period. If a subject is rescreened, data from a prior screening (e.g., food challenge results) may be included although the data is outside of the screening period just prior to baseline.

- **Pre-Maintenance Period:** This period is subsequent to the Screening Period and will commence when a subject has satisfied all screening criteria and is randomized to receive the first in-clinic dosing of the study drug. The visit and date for this period will be considered the "Day 1 (Baseline)" visit and date from the Suvoda IRT system for dosing data or the baseline visit determined for each subject in other data domains. However, the end date of this period will differ per study subject resulting to different duration of this period per study subject. The end date for this period will be 1 day prior to the date of first dose of the sequence of maintenance doses administered closest to the first Exit Food Challenge/Week 40 Visit assessment. The visits, dates and data corresponding to this period will be the visits, dates and data from each data domain that falls into the start and end dates of this period. For occurrence datasets such as adverse events and concomitant medications, the events or medications recorded with the start dates that fall into the start and end dates of this period, will be classified into this period. If the duration of these events span multiple periods, they will be considered ongoing safety events.
- **Maintenance Period:** This period commences just after the Updosing ends. The maintenance dose will be received throughout this period. The start date for this period will be the date of first dose of the sequence of maintenance doses administered closest to the first Exit Food Challenge/Week 40 Visit assessment. The end date of this period will be one day just before the first Week 40 Visit assessment or early termination date (whichever is the earliest) for the subjects discontinued the study during the Maintenance Period. The visits, dates, and data corresponding to this period will be the visits, dates, and data from each data domain that falls into the start and end dates of this period. For occurrence datasets such as adverse events and concomitant medications, the events or medications recorded with the start dates that falls into the start and end dates of this period, will be classified into this period. If the duration of these events span multiple periods, they will be considered ongoing safety events.
  If the subject exits the study without achieving a maintenance dose, then a flag will be set to denote that the subject did not achieve a maintenance dose during the study. Subjects who achieve a maintenance dose will have the date/visit of the first dose of the maintenance dose recorded in the database as the first dose of maintenance dose of study drug.
- **Exit Food Challenge/Week 40 Visit:** The Exit Food Challenge/Week 40 Visit will be performed over multiple visits for up to 6 weeks of daily dosing of study drug (this period may be extended to up to 8 weeks if a subject requires > 6 food challenges). Daily dosing will occur during this period except when withhold purposely, e.g., during the day of a DBPCFC. Although this portion potentially spans over a 6 week period (this period may

be extended to up to 8 weeks if a subject requires > 6 food challenges), it is considered a single visit per the study design. The visit and date corresponding to this portion will be taken directly as the Week 40 visit and date from the Suvoda IRT system for dosing dataset or the Week 40 visit from other data domains. The end date will be the date of the last Exit DBPCFC. During the Exit Food Challenge/Week 40 Visit period, the subject will keep taking their maintenance level of study drug except on days when it is specifically withheld for study procedures. For occurrence datasets such as adverse events and concomitant medications, the events or medications recorded with the start dates that falls into the start and end dates of this period, will be classified into this period. If the duration of these events span multiple periods, they will be considered ongoing safety events.

Adverse events during the Exit Food Challenge/Week 40 Visit period may be summarized by two periods: (a) Exit DBPCFC during challenge, i.e., days when Exit DBPCFC tests were administered and (b) Exit DBPCFC off challenge, i.e., days when Exit DBPCFC tests were not administered, in order to differentiate potentially treatment emergent vs potentially DBPCPC procedure-related event rates.

- **EOT:** This portion commences immediately after the Week 40 visit (the last Exit DBPCFC). Per the schedule of assessments, it covers an additional up to 4 weeks of daily blinded treatment after the last Exit DBPCFC until the subject completes treatment through the EOT visit. Although this portion spans over an up to 4 week period, it is considered a single visit per the study design. The visit and date corresponding to this portion will be taken directly as the EOT visit and date from either the Suvoda IRT system for doing dataset, or the EOT visit from other data domains. For occurrence datasets such as adverse events and concomitant medications, a start date of the last Exit DBPCFC plus 1 day and an end date using EOT eCRF date will be used to classify data into this portion. If the duration of these events span multiple periods, they will be considered ongoing safety events.
- **Follow-Up Period:** This period commences after the EOT visit only for subjects who are ineligible for or do not wish to continue to the OLE study. They will receive instruction by the investigator about withdrawal from study drug and attend a follow-up visit 14 days from the EOT visit. This period is considered a single visit per the study design. The follow-up visit, date, and data corresponding to this period will be taken as the follow-up visit, date and data from the eCRF for each data domain. For occurrence datasets such as adverse events and concomitant medications, a start date of the (EOT eCRF date plus 1 day) and an end date using date of last contact from EOS eCRF date will be used to classify data into this portion. If the duration of these events span multiple periods, they will be considered ongoing safety events.

Unless otherwise stated in the analysis sections below, unscheduled visits will be included in data listings only.

## 6.5. Worse-case Summaries

For change from baseline to worst-case summaries relating to laboratory or efficacy data, all study data including multiple measurements and unscheduled results will be employed to determine a post-baseline worse case value.

## 6.6. Data Pooling

In general, data for the 2 placebo treatment groups (low/high dose) will be pooled together, and compared to the low- and high-dose ADP101 treatment groups.

## 6.7. Subgroups

Although the general analysis will be presented by treatment group, subgroup analysis of the primary and secondary endpoints may be provided for the following:

- Age Group (pediatric subjects ≥ 4 to < 18 years of age, and adult subjects ≥ 18 to ≤ 55 years of age) according to the randomization stratification. No hypotheses testing will be performed in adult group; only descriptive statistics will be provided for this group.
- Target Maintenance Dose Group includes subjects who achieved their assigned target dose during the treatment stage and maintained this dose through the Exit Food Challenge/Week 40 Visit. These subjects will be analyzed according to their randomized treatment dose as the following:
    - Subjects who reached 1500 mg of study drug (low-dose group) – Yes or No
    - Subjects who reached 4500 mg of study drug (high-dose group) – Yes or No

  Achievement of the target maintenance dose will be captured by a flag (Y/N) in the database. The target dose level may be the same as the maintenance dose level for those subjects who reach their target dose and maintain it for at least two weeks prior to the Exit Food Challenge/Week 40 Visit.

# 7. Statistical Methods

## 7.1. Subject Disposition

Subject screened and screen failures will be presented using the Screened Population, including:

- Number of subjects screened as determined using the informed consent eCRF.
- Number of subjects screen failed as determined using the screen failure eCRF(s).

Other data in subject disposition will be presented using all randomized subjects. The following summary will be provided:

- Number (%) of subjects randomized as determined using the randomization eCRF.
- Number (%) in each analysis population (See Section 5).
- Number of subjects who received at least one dose of study drug
- Number of subjects who completed treatment as determined using the End of Treatment eCRF.
- Number (%) of subjects who terminated treatment and primary reasons for treatment termination as determined using the End of Treatment eCRF.
- Number (%) of subjects planning to continue in the OLE study as determined using the End of Study eCRF.
- Number (%) of subjects who completed study as determined using the End of Study eCRF.
- Number (%) of subjects who did not complete the study as determined using the End of Study eCRF.

Subject disposition will be listed, including but not limited to informed consent, inclusion and exclusion criteria, screen failure, and randomization eCRF plus Suvoda IRT randomization information.

## 7.2. Protocol Deviation

A major protocol deviation is a deviation from the Institutional Review Board (IRB) approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, major deviations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

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

The outline and details in capturing protocol deviations will be reported in the Protocol Deviation and Non-Compliance Management Plan (PDNCP).

The data will be managed in Clinical Trial Management System (CTMS). The list of protocol deviations will be reviewed by Alladapt, the medical monitor, and the study statistician and finalized before database lock of the study. The protocol deviation criteria will be graded as major or minor by Investigator or designee and the medical monitor. Protocol deviations that will affect inclusion into the analysis sets will be identified according to the details provided in the PDNCP. The final protocol deviations file from CTMS reviewed and approved by Alladapt will be used to create a protocol deviations SAS dataset for the final analysis.

A summary of major protocol deviations (including COVID-19 related deviations) by category (concomitant medication, inclusion or exclusion criteria, informed consent, investigational product, subject privacy, randomization, study procedure, COVID-19, etc.) will be presented using the ITT Population. A listing will be provided for all major and non-major protocol deviations.

If there is sufficient applicable data, a summary of COVID-19 related deviations by category will be presented using the ITT Population. A listing of COVID-19 related deviations will be provided.

### 7.3. Demographic and Baseline Characteristics

The demographics and baseline characteristics will be presented using the ITT Population and PP Population. The Demographics and baseline characteristics will be summarized using either continuous or categorical descriptive statistics and will include, but not limited to, the following variables:

- Age at screening (years), as collected on the eCRF.
- Sex.
- Childbearing potential if female.
- Race.
- Ethnicity.
- Height (cm) at Screening.
- Weight (kg) at Screening.
- Body Mass Index (BMI, $kg/m^2$) at Screening.
- Results from the SPT (mm) at screening (conducted prior to DBPCFC) for each of the 15 food sources overall and by food categorization (qualifying reactive, non-qualifying reactive, or non-reactive).
- $FEV_1$ percent predicted (%) at screening only for subjects aged 6 years or older (prior to the series of DBPCFCs.
- PEF (L/min) at screening only for subjects aged 4 to <6 years prior to the series of DBPCFCs.
- PEFR (L/min) at screening prior to the series of DBPCFCs.
- Assessment of asthma (Yes/No). For subjects with asthma, baseline severity using NHLBI will be summarized.

- Total immunoglobulin E (IgE), Total immunoglobulin G subclass 4 (IgG4), and Total IgE/IgG4 ratio and Total IgG4/IgE ratio at screening prior to the series of DBPCFCs.
- sIgE, sIgG4, sIgE/IgG4 ratio, and sIgG4/sIgE ratio for each food source prior to the Screening DBPCFCs overall and by food categorization (qualifying reactive, non-qualifying reactive, or non-reactive).
- Subjects with food allergies based on Screening DBPCFCs, including:
    - Qualifying, reactive foods: subjects with 1, 2, 3, 4, or 5 food allergies; subjects for individual food allergy
    - Non-qualifying, reactive foods: subjects with 1, 2, 3, 4, 5 or > 5 food allergies; subjects for individual food allergy

The following calculations will apply, if applicable:

- Height (in cm) = height (in inches) × 2.54.
- Weight (in kg) = weight (in lbs) × 0.4536.
- BMI (in kg/m²) = weight (in kg)/ height (in m)².

Subject data listings for demographics, baseline characteristics, screening SPT results for 15 food sources, screening spirometry results, baseline asthma assessments, and screening biomarker results will be provided using the Screened Population.

### 7.4. Medical/Surgical History

Medical/surgical history information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later.

The number and percentage of subjects will be summarized by system organ class (SOC) and preferred term (PT) using the ITT Population. The incidences will be presented by SOC in descending order for the total column and then, within a SOC, by PT in descending order for the total column.

All medical history data will be listed.

### 7.5. Allergy History

Data for allergy history will be collected in Entry Diet/Food Allergy Status & Entry Allergy Status for Other Allergies eCRFs. All allergy history data will be listed.

**Food Allergies to ADP101 Foods**

The number and percentage of subjects who perform entry food allergy assessment, and status/exposure (No Allergy Suspected [NAS], Allergy Suspected [AS], No Prior Exposure [NPE]) under each diet/food will be summarized and presented using the ITT Population.

In addition, the number and percent of subjects with food allergy to each ADP101 food source will be summarized for allergy status (NAS, AS, or NPE) versus SPT positive/negative, and allergy status versus food categorization (qualifying reactive, non-qualifying reactive, or non-

reactive) using the Screened Population. The allergy status will be indicated on the Entry Diet/Food Allergy Status eCRF; the SPT positive refers to the SPT result >3 mm, and the SPT negative refers to the SPT result ≤3 mm on the Entry Skin-Prick Tests For 15 Food Sources in ADP101 eCRF; the qualifying reactive, non-qualifying reactive, or non-reactive will be shown on the eCRF for Categorization of Individual Foods in ADP101 Based On Study Entry Results of DBPCFC.

**Other Allergies**

Other allergies such as pollen, insect bites (stingers), dander and epithelia (e.g., cats, dogs, mites and cockroaches), and other food allergies like lobster, fruits, vegetables and spice will be presented in a data listing using the ITT Population.

## 7.6. Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) B3 September 2020 version or later.

Subject incidence will be tabulated by Anatomic Therapeutic Class (ATC) level 2 and preferred term (PT), by treatment group and overall using the Safety Population. Subjects will be counted only once for each ATC level 2 or PT if they have multiple records of the same ATC or PT in the database. The incidences will be presented by ATC in descending order for the total column and then, within an ATC, by PT in descending order for the total column.

Medications detailed below will be summarized separately using the Safety Population.

All medications will be presented in by-subject data listings.

**Prior and Concomitant Medications**

Prior medication is defined as any medication received prior to the beginning of screening. Concomitant medication is defined as any medication continued or newly received at or after the beginning of screening. If a prior medication continues on or after screening, this prior medication will also be a concomitant medication.

Prior medications and concomitant medications will be summarized by treatment group.

**Rescue Medications**

For allergic reactions to food allergens that may occur during the DBPCFCs, subjects will be treated with epinephrine at the discretion of the investigator. Treatment of allergic reactions during the DBPCFCs, study drug dosing, and SPT may also require antihistamines, IV fluids, beta-adrenergic agonist (e.g., albuterol), oxygen, corticosteroids, and/or epinephrine, as indicated. Rescue medications will be identified by Yes responses to the Rescue Medication Question on the prior and concomitant medications source data.

These rescue medications will be summarized using the Safety Population. Rescue medications will also be summarized for Screening, Pre-Maintenance, Maintenance, Exit Food Challenge/Week 40 Visit, and Follow-Up Period.

**Concomitant Procedures and/or Non-drug Therapies**

Concomitant procedures and/or non-drug therapies will be coded using MedDRA version 23.0 or later. All concomitant procedures and/or non-drug therapies data will be presented in a by-subject listing using the Safety Population.

### 7.7. Study Drug Exposure

Descriptive statistics for treatment exposure will be presented using the Safety Population. The treatment exposure will be summarized for pre-maintenance period, maintenance period, Exit Food Challenge/Week 40 Visit period, EOT and overall treatment period. The analysis will be repeated using ITT and PP Population if sufficiently different from Safety Population by more than 5% of study subjects. The following will be summarized:

- The treatment exposure (days) using exposure duration.
- The treatment exposure (days) by dose level using exposure duration.
- Cumulative dose of the study treatment (mg).
- The average daily dose of study treatment (mg)
- The number and percent of subjects with 1, 2, 3 or more unsuccessful dose increases (as defined in Section 6.2.6.2) during the pre-maintenance period.
- The number and percent of subjects with 1, 2, 3 or more dose decreases during the pre-maintenance period and/or the maintenance period.
- The number and percent of subjects with missing dose and the number of subjects with 1, 2, 3, ≥ 4–≤ 7, or > 7 doses missed.

### 7.8. Efficacy Analysis

All efficacy-related data including the primary, secondary, and exploratory endpoints will be listed.

#### 7.8.1. Primary Efficacy Endpoint and Analysis

The primary endpoint is a ≥600 mg desensitization response as determined by tolerating ≥600 mg of food protein at the Exit DBPCFC without dose-limiting symptoms for at least 1 qualifying food.

Any subject who does not meet this definition will be considered a non-responder.

Classification as a 1000 mg responder is defined similarly.

**Primary Analysis**

The primary analysis of the primary endpoint will be performed on pediatric subjects in the ITT Population by treatment group.

The number and percent of subjects with a ≥600 mg desensitization response will be reported by treatment group. The primary endpoint hypothesis of superiority of ADP101 over pooled placebo will be tested using the Fisher's exact test. The unadjusted p-values will be reported. The difference in the proportions of responders (ADP101 vs. pooled placebo) with Newcombe 95% CIs will be reported using PROC FREQ procedure in SAS® and the RISKDIFF option.

A sample SAS code for the proc freq is provided below:

```
Ods output PdiffCL=pdiff
Proc freq
        data=indata;
        TABLE trtgrp*endpoint/ chisq riskdiff(cl=( newcombe ) correct );
        OUTPUT out=outdata CHISQ RDIF1 ;
RUN;
```

In order to handle the comparison of multiple active groups versus pooled placebo, the overall type-I error will be controlled by the use of the Simes global test (Simes, 1986) with the Holm procedure (Holm, 1979) to adjust for and test the global (joint) hypothesis that at least one of the 2 hypotheses below is rejected.

- $H_{01}$: proportion of responders in pooled placebo group = proportion of responders in low-dose (1500 mg) group
- $H_{02}$: proportion of responders in pooled placebo group = proportion of responders in high-dose (4500 mg) group.

The adjustment for multiplicity for the joint hypothesis in support of the primary efficacy endpoint will be performed using the PROC MULTTEST procedure in SAS® (HOLM option). The adjusted p-values will be reported along with the unadjusted p-values described above.

All efficacy-related data will be listed. Tables for the primary efficacy endpoint will include proportion of responders who tolerated at least 600 mg in pooled placebo vs low dose group and pooled placebo vs high dose group in ITT. The unadjusted and adjusted p-values will be displayed.

**Sensitivity Analysis**

To assess the robustness of the results in the primary analysis of the primary endpoint using the ITT Population, the following sensitivity analyses will be performed:

1. The primary endpoint will be analyzed for pediatric subjects in the ITT Population using logistic regression model including other factors such as age (years), gender, race, number of food allergies, eliciting dose (median eliciting dose for multiple qualifying foods) at baseline, etc.
2. The same analysis as described in the primary analysis above will be performed using the PP Population.

3. The same analysis as described in the primary analysis above will be performed on the subset of the PP Population that will exclude subjects who discontinue study drug prematurely due to treatment-related or unrelated reasons depending on their exit food challenge status.
4. The same analysis as described in the primary analysis above will be performed on the ITT Population excluding subjects who withdrew from the study prior to completing the Exit DBPCFC for reasons related to COVID-19 (e.g., study site closure).

If 2 or more subjects have missing data, the following sensitivity analyses may be performed:

1. The primary efficacy endpoint will be analyzed using a worst case approach to missing data imputation. Placebo subjects who have missing data (i.e., do not have an Exit DBPCFC) for the primary efficacy endpoint for any reason will be considered responders while ADP101 subjects will be considered non-responders if they have missing data for the endpoint. Analysis methods will follow those described above.
2. If the primary analysis of the primary endpoint shows a statistically significant treatment effect, a tipping point analysis will be conducted to identify the point at which the treatment effect becomes non-significant based on increasing the number of placebo subjects with missing data who are considered responders. The first step will be to test the treatment effect when all ADP101 subjects with missing data are considered non-responders and only one placebo subject with missing data is considered a responder while the remaining placebo subjects with missing data are considered non-responders. If that test shows a statistically significant treatment effect the number of placebo subjects who have missing data that are considered responders will be increased by one until the treatment effect becomes non-significant.

**Supportive Analyses**

In addition to the analyses described above, the following supportive analyses will be performed using the primary endpoint:

- The Farrington-Manning non-inferiority test will be used to compare the primary endpoint response rates of high-dose ADP101 vs. pooled placebo and low-dose ADP101 vs. pooled placebo using a margin of inferiority of 15%.
- The comparison of the primary endpoint between the pooled ADP101 vs. pooled ADP101 will be provided using the Fisher's exact test.
- The analysis of the primary endpoint will be performed for 2 additional populations, 1) all subjects (pediatric and adult subjects combined) and 2) adult subjects in the ITT Population. The same method as described in the primary analysis above (for pediatric subjects) will be used for all subjects and the unadjusted p-values will be reported. Descriptive statistics corresponding to the primary endpoint response rates will be reported for adult subjects.

The plots of subjects with a ≥600 mg desensitization response will be provided for pediatric, adult and all subjects in the ITT population and pediatric subjects in the PP population.

**Subgroup Analysis**

Subgroups of ITT subjects who reached their target dose as their maintenance dose (see Section 6.7) will be analyzed for the primary endpoint. The subjects with ≥600 mg desensitization response by reached target dose will be plotted for pediatric subjects in the ITT population.

The 15 ADP101 individual foods will be consolidated into 9 foods/food groups, including peanut, tree nuts (almond, cashew, hazelnut, pecan, pistachio, or walnut), milk, egg, soy, wheat, shrimp, finfish (codfish or salmon), and sesame. Descriptive statistics, such as response rate differences and corresponding 95% CIs, will be provided for each ADP-101 food/food group above as long as there is sufficient sample size in that food/food group. The response rate for each food/food group will be based on the number of subjects with qualifying food allergies within the category.

**Supplemental Analyses using the Estimand Framework**

The primary and top secondary endpoint will be analyzed using the Estimand framework outlined in the E9(R1) (Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials) guidance. The intercurrent event of interest is study discontinuation without completing the exit DBPCFC for any of the subject's qualifying food allergies.

| **Intercurrent event = Study discontinuation prior to week 40 Exit DBPCFC** | **Strategy for Addressing the Intercurrent Event Type and its Description** |
|---|---|
| Type A: Study discontinuation due to AE | Treatment Policy Strategy: impute using J2R (jump to reference) by setting to non-responder to each qualifying food |
| Type B: Study discontinuation due to administrative reasons including COVID-related site closure, summer camp attendance or academic reasons | Treatment Policy Strategy: impute using J2R by setting to non-responder to each qualifying food<br>Hypothetical Strategy: impute using subject's respective treatment group's response rate |
| Type C: Study discontinuation due to fatigue, taste, texture or volume of IP | Treatment Policy Strategy: impute using J2R by setting to non-responder to each qualifying food<br>Hypothetical Strategy: impute using subject's respective treatment group's response rate |

The analyses will be done where (i) each type of study discontinuation will be analyzed using the Treatment Policy Strategy, (ii) each type of study discontinuation will be analyzed using the Hypothetical Strategy and (iii) a Hybrid Strategy where Type A and C will be analyzed using

Treatment Policy and Type B will be analyzed using Hypothetical Strategy, as well as (iv) a Hybrid Strategy where Type A will be analyzed using Treatment Policy and Type B will be analyzed using Hypothetical Strategy.

### 7.8.2. Secondary Efficacy Endpoints and Analysis

The primary analysis of the secondary endpoints will be performed on pediatric subjects in the ITT Population by treatment group. The analysis will be repeated for the PP Population and relevant subgroups (i.e., subjects who reached 1500 mg of study drug for low-dose group, and subjects who reached 4500 mg of study drug for high-dose group). The analysis will be repeated for all subjects in the ITT Population as well. Descriptive statistics corresponding to the endpoint response rates will be provided for adult subjects. The secondary endpoints will also be analyzed for pediatric subjects in the ITT Population using logistic regression model. The comparison of the secondary endpoints between the pooled ADP101 vs pooled ADP101 will be provided as well.

The secondary endpoints are outlined below:

- Number and percent of subjects who tolerate the 1000-mg level of a single Qualifying Food without dose-limiting symptoms at the Exit DBPCFC (i.e., ≥1000 mg desensitization response)
- Number and percent of subjects with ≥ 2 qualifying FAs who tolerate the 600-mg level of each of 2 or more Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC
- Number and percent of subjects with ≥ 2 qualifying FAs who tolerate the 1000-mg level of each of 2 or more Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC

The analyses of the secondary efficacy endpoints will follow the method of the primary efficacy endpoint as described in Section 7.8.1. For these analyses, only the p-values from the Fisher's exact test will be displayed.

The same analyses will be performed on the ITT Population excluding subjects who withdrew from the study prior to completing the Exit DBPCFC for reasons related to COVID-19 (e.g., study site closure).

The last two endpoints will be conducted in the ITT Population, PP Population and relevant subgroups for multi-allergic subjects only.

The plots of each secondary endpoint will be provided for pediatric, adult and all subjects in the ITT population and pediatric subjects in the PP population. The subjects with ≥1000 mg desensitization response by reached target dose will be plotted for pediatric subjects in the ITT population.

### 7.8.3. Exploratory Endpoints and Analysis

Unless otherwise specified, the analysis of exploratory endpoints will be performed in pediatric subjects using the ITT Population; the analysis will be repeated for all subjects; if the PP Population is sufficiently different from the ITT Population by more than 5% of study subjects, the analysis may be repeated for pediatric subjects in the PP Population.

#### 7.8.3.1. Characterizing Response in Multiple Food Allergies

Descriptive statistics will be provided for the following for each treatment group:

- Number and percent of subjects with 1 or more qualifying FAs who tolerate the 600-mg level of majority of the Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC
- Number and percent of subjects with 1 or more qualifying FAs who tolerate the 1000-mg level of majority of the Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC
- Number and percent of subjects with 1 or more qualifying FAs who tolerate the 600-mg level of all of the Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC
- Number and percent of subjects with 1 or more qualifying FAs who tolerate the 1000-mg level of all of the Qualifying Foods without dose-limiting symptoms at the Exit DBPCFC

The summaries above will also be present by the number of qualifying FAs.

Figures will be provided to display the endpoints above by treatment group.

#### 7.8.3.2. Maximum Tolerated Dose (MTD)

**Qualifying Food Allergies (FAs)**

For the MTD in qualifying FAs, the following imputation will apply to the endpoints:

- Subjects who do not undergo the Exit DBPCFC have the MTD for the Exit DBPCFC imputed as the MTD at the Screening DBPCFC for the subjects' individual qualifying FAs.
- In order to calculate fold increase of the MTD at the Exit DBPCFC relative to the Screening DBPCFC, if subjects do not tolerate any dose level they will be assigned an MTD of 1 mg.

The following categorical endpoints will be summarized by frequency and percentages of subjects achieving the endpoint for each treatment group.

- Each level of MTD achieved for each qualifying FA at Screening and Exit DBPCFC
- Each level of the relative (fold) increase in MTD from Screening DBPCFC to Exit DBPCFC for each qualifying FA

- Number and percent of subjects with the Exit DBPCFC MTD greater than the Screening DBPCFC MTD for each ADP101 food source based on subjects with corresponding qualifying food allergies
- Number and percent of subjects with the Exit DBPCFC MTD greater than the Screening DBPCFC MTD for at least one food in each ADP101 food/food group (peanut, tree nut, milk, soy, wheat, sesame, finfish, shrimp, and egg) based on subjects with corresponding qualifying food allergies.

The following endpoints will be provided descriptively (median, first and third quartiles [Q1:Q3], min and max) by treatment group.

- Actual value and fold change of MTD between the screening DBPCFC and the Exit DBPCFC of each individual qualifying FA
- Actual value and fold change of the eliciting dose between the screening DBPCFC and the Exit DBPCFC of each individual qualifying FA

Box plot will be provided for MTDs and eliciting doses at the Screening and Exit DBPCFCs across qualifying FAs.

**Non-Qualifying Reactive Food Allergies**

For non-qualifying reactive FAs, if both screening and exit DBPCFC results are present, the fold increase in MTD from Screening DBPCFC to Exit DBPCFC for that non-qualifying reactive food will be summarized using both continuous and categorical descriptive statistics as described above for qualifying reactive foods.

Similar summary will be provided for eliciting dose.

Box plot will be provided for MTDs and eliciting doses at the Screening and Exit DBPCFCs across non-qualifying reactive FAs.

#### 7.8.3.3. Neo-Sensitization

Neo-sensitization is defined as subjects who develop confirmed new FAs to previously Non-reactive Foods at Screening, as demonstrated by the Exit DBPCFC.

To determine which subjects would have Exit DBPCFCs on FAs non-reactive at screening, see Figure 4.

The number and percentages of subjects who meet neo-sensitization criteria at any dose level will be summarized by treatment group. As appropriate, the proportions of subjects with neo-sensitization in each ADP101 group versus the pooled placebo group will be compared using the Fisher's exact test. The p-values will be provided. For each food source, the number and percentages of subjects with neo-sensitization at each dose level may be provided as well. The plot of subjects with neo-sensitization at any dose level for any food will be provided.

#### 7.8.3.4. Biomarkers for Each Food Allergy

Serum samples to measure sIgE and $sIgG_4$ for each food, total IgE and total $IgG_4$ will be collected prior to the Screening DBPCFCs, Week 20 and Week 38 (prior to the Exit DBPCFCs). The specific and total IgE/$IgG_4$ and $IgG_4$/IgE ratios will be calculated, listed by subject, and summarized by visit and treatment group. Analyses will be performed on pediatric subjects in the ITT Population and PP Population by treatment group. The analysis will be repeated for all subjects by treatment group.

Results outside the limits of quantification will be displayed as less than the lower limit of quantification (LLOQ), or greater than the upper limit of quantification (ULOQ), as appropriate. These values will be summarized as either the LLOQ or the ULOQ. If the IgE or IgG4 is outside of the limits of quantification, the IgE/IgG4 or $IgG_4$/IgE ratio will be set as missing.

Summary statistics, including mean, SD, geometric mean and geometric coefficient of variation (CV), median, min and max, will be presented for actual values and change from baseline, by time point and treatment group for each biomarker. The sIgE, $sIgG_4$, and their ratios will be summarized for qualifying and non-qualifying reactive foods, as well as non-reactive foods. The graphs of mean (SD) actual value and change from baseline in each biomarker over time will be provided.

Biomarker results will be listed.

#### 7.8.3.5. Skin-Prick Test

The SPT data for all 15 food sources will be collected prior to the Screening DBPCFCs, Week 38 or at the Early Termination (ET) visit. Analyses will be performed on pediatric subjects in the ITT Population and PP Population by treatment group. The analysis will be repeated for all subjects by treatment group.

Actual values and change from baseline of SPT mean wheal diameter (relative to negative control) will be summarized at all time points for qualifying and non-qualifying reactive foods as well as non-reactive foods using descriptive statistics. The graphs of mean (SD) value and change from baseline in SPT mean wheal diameter (relative to negative control) over time will be provided.

The number and percentage of subjects with a mean wheal diameter $\leq 3$ mm or $> 3$ mm will be presented for each food source and each timepoint.

SPT results will also be listed.

#### 7.8.3.6. Use of Epinephrine as a Rescue Medication

Per protocol, subjects have ready access to 2 nonexpired epinephrine autoinjector (EAI) devices at all times during the study. Epinephrine use as a rescue medication for AEs will be identified from the concomitant medication dataset as medications with a preferred name of

"EPINEPHRINE" indicated as a rescue medication on the concomitant medication eCRF, and reported as adverse event of special interest (AESI) in the AE eCRF.

The number and percent of subjects using epinephrine as a rescue medication for AEs at the Screening and Exit DBPCFCs, and the Pre-Maintenance, Maintenance and EOT will be summarized by treatment group. The number and percent of subjects using epinephrine as a rescue medication by number of epinephrine uses per subject (1, 2, 3, 4, and 5 or more) will be provided as well. Multiple uses per day per subject will be considered a single use. For the Pre-Maintenance, Maintenance and EOT, the number and percent of subjects using epinephrine as a rescue medication will be presented by the event prompting epinephrine use (e.g., accidental exposure, and study drug related), and the maximum severity of AEs prompting epinephrine use will be summarized.

The subjects with epinephrine use at the Screening and Exit DBPCFCs will be plotted by treatment group. The plot of subjects with epinephrine use at the Screening and Exit DBPCFCs by number of epinephrine uses per subject will be provided as well.

#### 7.8.3.7. Quality of Life Assessments

**Food Allergy Quality of Life Questionnaire**

The FAQLQ is a disease specific health-related quality of life (HRQoL) questionnaire of both subjects and their families.

It will be completed by study subjects 8 years old and older: FAQLQ-Child Form for age range 8 to 12 years old; FAQLQ-Teenager Form for age range 13 to 17 years old; and FAQLQ-Adult Form for age range 18 to 55 years old.

Parents will also complete a FAQLQ for subjects 4 to 12 years old (FAQLQ-Parent Form) and for subjects 13 to 17 years old (FAQLQ-Parent Form Teenagers).

These will be completed prior to the Screening DBPCFCs, Week 20, prior to the Exit DBPCFCs and at the EOT or ET visits. The same questionnaire will be completed throughout the study according to the subject's age at Screening.

The number of items and domains varies by instrument administered. Each version contains 3 or 4 domains to assess different aspects of FA-related (HRQoL).

| Questionnaire | Domains | Number of Items |
|---|---|---|
| FAQLQ-CF | Allergen Avoidance, Dietary Restrictions, Emotional Impact, and Risk of Accidental Exposure | 24 |
| FAQLQ-TF | Allergen Avoidance, Dietary Restrictions, Emotional Impact, and Risk of Accidental Exposure | 23 |
| FAQLQ-AF | Allergen Avoidance, Dietary Restrictions, Emotional Impact, Risk of Accidental Exposure, and Food Allergy–Related Health | 29 |
| FAQLQ-PF | Emotional Impact, Food-Related Anxiety, and Social and Dietary Limitations | 30 |

Abbreviations: AF = Adult Form; CF = Child Form; FAQLQ = Food Allergy Quality of Life Questionnaire; PF = Parent Form; TF = Teen Form.

Each question item employs a seven-point response scale rating from 0 (no impairment) to 6 (maximal impairment) for each FAQLQ questionnaire. The total FAQLQ scores and domain scores are calculated by dividing the sum score of completed items by the number of completed items. Missing data will not be imputed. If less than 80% of the items within each of the total FAQLQ and domain are complete, then the total score and/or the domain score will not be calculated and set as missing.

The total and domain scores of each questionnaire type will be summarized for pediatric subjects and all subjects by treatment group at each time point using actual value and change from baseline results.

Listing of the raw scores as recorded in the eCRF will be provided, sorted by treatment group and subject ID.

**Food Allergy Quality of Life Parental Burden Questionnaire**

Assessment of FAQL-PB will be performed prior to the Screening DBPCFCs, Week 20, prior to the Exit DBPCFCs, and at EOT or ET.

The FAQL-PB questionnaire is a self-administered 17-item questionnaire developed to measure the burden on parents with food-allergic children aged 0 to 17 years. The questionnaire contains 2 domains, emotional distress and limitation on life, that include 14 (questions 4 to 17) and 3 (questions 1 to 3) items, respectively. Each item uses a 7-point response option rating from not troubled (or not limited) to extremely troubled (or limited).

The domain scores for (emotional distress and limitation on life) which is a sum of the scores for each question within each domain will be calculated and summarized using descriptive statistics. The total score which is the sum of all the scores from all the 17 questions will also be summarized using descriptive statistics.

Listing of the raw FAQL-PB scores as recorded in the eCRF as well as the derived domain and total scores will be provided, sorted by treatment group and subject ID.

**Treatment Satisfaction Questionnaire for Medication**

Assessment of treatment satisfaction will be performed using the TSQM-9 at Week 20, prior to the Exit DBPCFCs, and at EOT or ET. It will be completed by the subject (or the parent for children < 12 years of age).

The TSQM-9 is a widely used instrument to assess treatment satisfaction with medication in studies where subject reported side effects have a potential to interfere with the objectives of the study. The instrument consists of 9 questions representing 3 domains: effectiveness, convenience and global satisfaction that together provide a measure of treatment satisfaction with medication from a subject's perspective. Each of the 3 domains contains 3 items. The Effectiveness scale

includes items 1-3, the Convenience scale includes items 4-6, and the Global Satisfaction scale includes items 7-9. Each item uses a 7-point response option listed as extremely dissatisfied (or inconvenient, difficult) to extremely satisfied (or convenient, easy). Items 7 and 8 have 5 response options that range from not at all confident (or not certain) to extremely confident (or certain). The scores for each TSQM-9 range from 0 to 100, with higher scores representing higher satisfaction on that domain. Each scale will be scored as: 100*[(sum of non-missing responses) minus the number of non-missing responses] divided by the maximum possible score of the sum of non-missing responses. If more than one item within the scale has a missing result then the scale score will not be calculated.

The scale scores (effectiveness, convenience, and global satisfaction) will be calculated and summarized using descriptive statistics.

Listing of the raw TSQM-9 scores as recorded in the eCRF as well as the derived scale scores will be provided, sorted by treatment group and subject ID.

**Accidental Exposure Questionnaire**

The occurrence of a safety event associated with accidental food ingestion will be reported as a food allergy episode, as per the protocol. Even if the subject does not have a reaction, the accidental exposure need still be reported. Any such event that meets the definition of an AE or SAE will also be reported as an adverse event. Incidence of accidental exposure will be collected throughout the study from the Baseline/Day 1 visit through the EOT visit.

The Accidental Exposure Questionnaire is a newly-developed self-administered questionnaire containing 11 items asking about known food allergen exposure, associated symptoms experienced (if any), and treatment received (if any) following accidental exposure to a food to which the subject is allergic. It will be completed by the subject (or the parent in the case of children < 12 years of age) immediately following any incident of accidental exposure to the known allergic food(s). Instances in which exposure is intentional, such as during study drug dosing-related exposure, are not considered accidental exposures and will not prompt use of this questionnaire. Subjects (or their parents) may use a mApp to complete the questionnaire to ensure a timely assessment of accidental exposure and its consequences.

The analysis of this endpoint will be performed by treatment group and by study period (Overall, Pre-Maintenance, Maintenance, Exit Food Challenge/Week 40, and EOT). For each period, the number of subjects experiencing any accidental exposure instance, the number of subjects experiencing accidental exposure instances in response to food source, the number of instances of each food source experienced per subject, the total number of food source instances, and the number of subjects experiencing any accidental exposure instances with and without symptoms.

All accidental exposure data will be listed by age group, treatment group, and subject.

**Immunotherapy-Related Quality of Life Questionnaire**

Assessment of IQoL will be collected prior to Screening DBPCFCs, Week 20, prior to Exit DBPCFCs, and at EOT or ET.

The IQoL is a newly developed questionnaire designed to assess aspects of HRQoL affected by living with an FA. In contrast to the FAQLQ, the IQoL aims to assess perceived impairment resulting from allergy to foods specifically treated by OIT. The IQoL assesses constructs identified by OIT-treated subjects as contributing to psychosocial burden in the context of their food allergen immunotherapy. The IQoL has versions for children aged 8 to 12 years (18 items) and teens/adults aged ≥ 13 years (23 items), and a proxy version for parents of children with FA aged 4 to 17 years (23 items). The IQoL measures nervousness or worry about being exposed to OIT-treated food allergens, social limitations, and emotional impact. Due to the novelty and ongoing development of the IQoL, psychometric validation analyses will be conducted as part of this study to confirm its structure and psychometric properties. The scoring algorithm will be determined during the validation process.

| **Questionnaire/Domain** | **Number of Items** |
|---|---|
| IQoL -CF | 18 |
| IQoL –TF/AF | 23 |
| IQoL -PF | 23 |

Abbreviations: AF = Adult Form; CF = Child Form; IQoL = Immunotherapy-Related Quality of Life Questionnaire; PF = Parent Form; TF = Teen Form.

Each question item employs a 5-point response scale rating of either (Never, Rarely, Sometimes, Often, Always) for emotional impact question or (Not at all, A little bit, Somewhat, Quite a bit, Very much) for all others.

The process of scoring this questionnaire is provided below.

- Step 1: Assign the following scores to the responses: Not at all/ Never = 0; A little bit /Rarely = 1; Somewhat /Sometime = 2; Quite a bit/ Often =3; Very much / Always = 4

- Step 2: Check for missing Items: Scoring requires 75% completion of items for analysis

| **Age Specific IQoL** | **Subdomain: Worry/Expectation of Adverse Outcome** | **Subdomain: Emotional Impact** | **Subdomain: Social Impact** | **Total IQoL Score** |
|---|---|---|---|---|
| Teenager/Adult And Parent | 5/7 items | 8/11 items | 4/5 items | 18/23 items |
| Child | 4/5 items | 6/8 items | 4/5 items | 14/18 items |

- Step 3: Calculate the following scores when data requirements are met
  - Total IQoL score within each of the 3 questionnaires

- Total score for each of the 3 subdomains within each of the 3 questionnaires as given below.

| **Age Specific IQoL** | **Subdomain: Worry/Expectation of Adverse Outcome** | **Subdomain: Emotional Impact** | **Subdomain: Social Impact** |
|---|---|---|---|
| Teenager/Adult | 7 items: 1,2,3,4,5,6,23 | 11 items: 7, 8, 9, 10, 12, 13, 15, 17, 18, 21, 22 | 5 items: 11, 14, 16, 19, 20 |
| Child | 5 items: 1, 2, 3, 4, 18 | 8 items: 5, 6, 8, 9, 11, 13, 14, 17 | 5 items: 7, 10, 12, 15, 16 |
| Parent | 7 items: 1, 2, 3, 4, 5, 6, 23 | 11 items: 7, 8, 9, 10, 12, 13, 15, 17, 18, 21, 22 | 5 items: 11, 14, 16, 19, 20 |

The total and subdomain scores of each questionnaire type will be summarized for pediatric subjects and all subjects by treatment group at each time point using actual value and change from baseline results.

Listing of the raw IQoL scores as recorded in the eCRF and derived scores will be provided, sorted by treatment group and subject ID.

**Asthma Control Test or Childhood Asthma Control Test Questionnaire**

For subjects with asthma, the asthma control test (ACT) (subjects ≥12 years of age) or childhood ACT (C-ACT) (children 4 to 11 years of age) will be collected prior to Screening DBPCFCs, Week 20, prior to Exit DBPCFCs, and at EOT or ET.

The ACT is a 5-item, subject-based, clinically validated assessment of asthma control, designed to measure dimensions of asthma control outlined in the current asthma management guidelines as defined by the NHLBI: asthma symptoms, utilization of rescue medications, and impact of asthma on everyday functioning. The ACT is a simple measure of assessing asthma control that is suitable for use with or without lung function testing. The ACT data entered on the eCRF will be automatically scored in real time via Medidata and Optum cloud-based platform, and provided as part of RAVE data extracts for SDTM data generation. The total score range from 5 (poorly controlled asthma) to 25 (well-controlled asthma). A total score of 19 or less indicates asthma is not adequately controlled. Missing data will not be imputed as the data are already scored accounting for missing data in the scoring algorithm used by Optum.

The C-ACT captures the frequency of asthma symptoms and their effect on daily function in children 4 to 11 years of age. It is composed of 7 items investigating one domain and consists of child completed items on a 4-point pictorial response, and parent/caregiver completed items on a 6-point Likert scale. The scoring of the C-ACT data is as follows:

- Step 1: Child responds to the first 4 questions (1 to 4).If the child needs help reading or understanding the question, the parent/caregiver may help, but should let the child select the response.
- Step 2: Parent/Caregiver complete the remaining three questions (5 to 7) on their own and without letting the child's response influence their answers. There are no right or wrong answers.
- Step 3: Parent/Caregiver write the number of each answer in the score box provided.
- Step 4: Parent/caregiver add up each score box for the total.
- Step 5: Parent/caregiver take the test to the doctor provider to discuss their child's total score.

The total C-ACT score provided by the parent/caregiver is entered on the eCRF. The total score range between 0 (poorly controlled asthma) and 27 (well-controlled asthma). A total score of 19 or less indicates asthma is not adequately controlled.

The total ACT or C-ACT scores will be summarized by treatment group at each time point using actual value and change from baseline results. A shift table of asthma control (adequate, not adequate, missing) will be summarized by treatment at each visit. The number of subjects with completed ACT/C-ACT questionnaires will be used as the denominator for all percentages.

Listing of the raw ACT and C-ACT scores as recorded in the eCRF and derived scores will be provided, sorted by treatment group and subject ID.

#### 7.8.3.8. Accidental Exposure

Based on the data in the accidental exposure questionnaire, the following accidental exposure endpoints will be summarized for each treatment group:

- Number and percent of subjects with any accidental exposures
- Number and percent of subjects with any accidental exposures requiring treatment
- Number and percent of subjects with any accidental exposures requiring epinephrine use
- Number and percent of subjects with any accidental exposures requiring hospitalization
- Number and percent of subjects with AEs due to accidental exposures

In addition, the accidental exposures will be summarized by period for each treatment group.

#### 7.8.3.9. Maximum Severity of Allergy Symptoms Assessed During DBPCFCs

The severity of symptoms will be assessed at Screening DBPCFCs and Exit DBPCFCs. Grading of symptoms will be done using the grading definition in the Oral Food Challenge (OFC) Symptom Score Sheets. Symptom severity will be determined at 6 levels: 0-None, 1-Mild, 2-Moderate, 3-Severe, 4-Life Threatening, and 5-Death. Subjects who experience no symptoms will be assigned a severity of 0-None. Symptom severity data will be collected at each challenge dose of food source during the Screening DBPCFCs (1, 3, 10, 30, 100, 300, 600, or 1000 mg) and the Exit DBPCFCs (1, 3, 10, 30, 100, 300, 600, 1000, 2000, or 4000 mg).

The maximum severity of symptoms observed in the DBPCFC at any dose ((screening: 1000 mg or lower) and (Exit Food Challenge/Week 40: 4000 mg or lower)) will be used for each subject in the analysis of this endpoint.

The number and percent of subjects by maximum severity at the Screening and Exit DBPCFCs for each qualifying food at any dose will be provided by treatment group. The summary will be repeated for non-qualifying reactive food at any dose level.

Severity of symptoms data will be listed.

The maximum severity of allergy symptoms at any dose and at each dose of the Screening and Exit DBPCFCs for each qualifying food will be graphically displayed, respectively.

#### 7.8.3.10. Maintenance Dose for Study Drug

The maintenance dose (mg/day) will be summarized by treatment group using descriptive statistics (median, min, max, and Q1:Q3). The number and percentage of subjects whose maintenance dose is 50, 100, 200, 400, 700, 1000, 1500, 3000, or 4500 mg/day will be provided as well. If a subject exits the study prior to achieving a dose of at least 50 mg, then the maintenance dose will be set to missing.

The time to achieving the maintenance dose level is defined as [(first dose date of maintenance dose) – (first dose date of study drug) + 1]. The maintenance dose for these individuals can be determined once the subject has started the exit challenge procedure (i.e. maintenance is the week 38 dose level), reached the target dose for their randomized treatment group or discontinued the study. The time to achieving first maintenance dose will be presented for the treatment period using Kaplan-Meier (KM) method. Subjects who do not reach a maintenance dose will be censored at the date of their last study drug dose. KM curves will be plotted separately for the pooled placebo, low-dose and high-dose groups. A similar method will be repeated for time to achieving target dose level (1500 mg/day for low-dose and 4500 mg/day for high-dose) as maintenance dose.

#### 7.8.3.11. Target Attainment

100% target attainment occurs when a subject attains the randomized target dose of 1500 mg/day for low-dose regimen or 4500 mg/day for high-dose regimen. A subject's target attainment at MD is expressed as a percentage, calculated as [(maintenance Dose) / (target dose level) × 100].

The number and percent of subjects who attained randomized target levels of 1500 mg/day (low-dose regimen) or 4500 mg/day (high dose regimen) by visit will be provided. The target attainment at MD will be summarized using continuous and categorical (e.g., 100%, ≥ 90% - < 100%, ≥ 80% - < 90%, < 80%) descriptive statistics. The proportion of subjects with 100% target attainment versus visit along with CI will be plotted. A swimmer plot showing individual exposure to study drug (in weeks) over time by treatment group and dose level, will also be provided.

## 7.9. Safety Analysis

All safety analyses will be performed using the Safety Population. Safety data in this study will include AEs, clinical laboratory data, vital signs, pulse oximetry, spirometry, physical examinations, and assessment of asthma severity using NHLBI criteria.

Unless otherwise noted, safety data will be summarized descriptively by treatment group for pediatric subjects and all subjects. Further breakdown by Screening Period, Pre-maintenance Period, Maintenance Period, Exit DBPCFC during challenge and Exit DBPCFC off challenge, EOT and Follow-Up Period will be provided for some AE summaries.

### 7.9.1. Adverse Events

All AEs will be coded and classified according to MedDRA version 23.0 or later. All nonallergic AEs will be graded according to the NCI CTCAE Version 5.0. All allergic AEs will be graded according to the Consortium of Food Allergy Research (CoFAR) grading scale, with Grade 1 (mild symptoms), Grade 2 (moderate symptoms), Grade 3 (severe symptoms), Grade 4 (life-threatening symptoms) and Grade 5 (death). The relationship of AE to study drug will be judged by the investigator as related or not related.

Treatment-emergent AEs (TEAE) are defined as any event that starts or worsens in severity on or after the first dose of study drug until 30 days after the last dose of study drug. TEAEs will be considered treatment-related if relationship information is missing. Similarly, TEAEs will be considered severe if the severity information is missing. Imputed values for relationship, severity or onset date will be used for incidence summaries, while the actual values will be used in data listings. The AEs not considered to be a TEAE will be included in subject listings, but not summarized.

The AESIs include the following categories: anaphylaxis, any AE leading to the use of epinephrine (e.g., EAI), and Eosinophilic Esophagitis (EoE).

All reported AEs will be classified into SOC and PT. Summaries will be ordered by descending incidence of SOC and PT within each SOC for the overall column. Summaries displayed by PT only will be ordered by descending incidence of PT for the overall column. In addition, exposure adjusted incidence rates of TEAEs, treatment-emergent serious adverse events (TESAEs) and treatment-emergent AESIs will be presented, where exposure incidence rate is defined as the total number of events divided by the total number of subject-years at risk during the study treatment period, or defined as the total number of events divided by the total number of study drug doses received during the study treatment period.

An overview summary of the number and percentage of subjects with at least one of the following AE categories will be presented by treatment group and overall.

- Any TEAE
- Any TESAE
- Any TEAE related to study drug

- Any TEAE due to accidental exposure
- Any TEAE due to food challenge
- Any TEAE due to other study procedure
- Any TESAE related to study drug
- Any TESAE due to accidental exposure
- Any TESAE due to food challenge
- Any TESAE due to other study procedure
- Any TEAE resulting in drug discontinuation
- Any TEAE resulting in drug interruption
- Any TEAE resulting in drug modification (i.e., dose decrease or increase)
- Any TEAE resulting in discontinuation from study
- Any TEAE with fatal outcome
- Any allergic TEAE
- Any allergic TEAE with Grade ≥3
- Any nonallergic TEAE with Grade ≥3
- Any AESI

The number and percentage of subjects with TEAEs/AEs will be summarized by SOC and PT for the following:

- TEAEs
- TEAEs by severity
- Allergic TEAEs
- Allergic TEAEs by severity
- Allergic TEAEs with CoFAR Grade 3 or higher
- Non-allergic TEAEs
- Non-allergic TEAEs by severity
- Non-allergic TEAEs with CTCAE Grade 3 or higher
- TEAEs related to study drug
- TEAEs due to accidental exposure
- TEAEs due to accidental exposure by severity
- AEs due to food challenge (at Screening and Exit DBPCFCs)
- TESAEs
- TESAEs related to study drug
- TEAEs resulting in study drug discontinuation
- TEAEs resulting in discontinuation from study
- Treatment-emergent AESIs by category

In addition, summaries of the following exposure-adjusted rates (per person-years and per total doses) will be provided:

- Exposure adjusted rates of TEAEs by PT
- Exposure adjusted rates of TEAEs related to study drug by PT

- Exposure adjusted rates of TESAEs by PT
- Exposure adjusted rates of treatment-emergent AESIs by PT
- Exposure adjusted rates of treatment-emergent AESIs related to study drug by PT

Subjects will be counted only once within each SOC and PT in the summary tables. For the summary tables by Grade ≥3, if the same TEAE (PT) is reported more than once for the same patient, the highest severity grade will be counted in the summary table.

The following AEs will also be summarized by study period with each AE counted once in the period where it started. The number of subjects with ongoing AEs in each period will be provided as well.

- Overall summary of AEs
- AEs by SOC and PT
- Allergic TEAEs with CoFAR Grade 3 or higher
- AESIs by SOC and PT
- Exposure adjusted rates of TEAEs by PT
- Exposure adjusted rates of treatment-emergent AESIs by PT

The subjects with any CoFAR grade ≥3 anaphylaxis and with any CoFAR grade ≥4 anaphylaxis will be presented in all AESI summary tables.

The following AEs will be presented as listings by subject:

- Nonallergic AEs
- Allergic AEs
- Serious AEs
- AEs resulting in study drug discontinuation, interruption, or modification
- AEs resulting in study discontinuationAESIs
- AEs with fatal outcome

### 7.9.2. Laboratory Assessments

Laboratory data, including hematology, chemistry and pregnancy test (Appendix 2), will be collected at Screening, Week 38, ET, and Follow-up as well as unscheduled visits as clinically indicated.

Laboratory test parameters for hematology and chemistry, with associated reference ranges provided by the laboratory, will be listed for individual subjects; out-of-reference-range (abnormal) values will be flagged as high (H) or low (L) in the listings; if applicable, the assessment of clinical significance will be noted and included in the listings. Human chorionic gonadotropin pregnancy test as needed for women of childbearing potential will be presented in a listing.

Observed values and change from baseline to each post-baseline visit in hematology and chemistry data will be summarized by treatment group for each age group and overall using

descriptive statistics for the Safety Population. Laboratory results obtained from unscheduled visits will not be included in the summary.

Shifts from baseline to post-baseline visit of test abnormality level (low, normal, high) with, if applicable, clinical significance will be provided.

Laboratory data will be summarized or listed in International System of Units (SI). For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively. The original laboratory values preceded by a "<" or a ">" sign are presented in the listing.

### 7.9.3. Vital Signs

Vital signs, including body temperature (ºC), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiration rate (breaths/min), heart rate (beats/min), and pulse oximetry (%), will be assessed at all study visits.

Descriptive summaries for observed data and changes from baseline will be calculated and summarized for each scheduled visit by treatment group for each age group and overall in the Safety Population.

If applicable, shifts from baseline to post-baseline visit of test abnormality level (low, normal, high) will be provided for each parameter.

The conversion for temperature is: temperature (in °C) = 5/9 (temperature [in °F] - 32).

Vital sign measurements with abnormal values flagged will be presented for each subject in a data listing.

### 7.9.4. Spirometry

Spirometry assessments including Forced Expiratory Volume (FEV1) only for subjects aged 6 years or older and Peak Flow Meter (PEF) for subjects aged 4 to < 6 years will be collected prior to Screening DBPCFCs, prior to Exit DBPCFCs, at ET and at unscheduled visits (if clinically indicated per the investigator's discretion).

Spirometry assessment of Peak Expiratory Flow Rate (PEFR) will be collected prior to Screening DBPCFCs, Baseline (Day 1), prior to Exit DBPCFCs, ET, unscheduled visit, as well as at other visits if clinically indicated per the investigator's discretion. Three attempts of PEFR are performed at any time, and the best (highest) value will be flagged in data listings. Only the best PEFR value will be summarized.

Descriptive summaries of observed data and changes from baseline will be calculated for the following spirometry parameters: $FEV_1$ (L), $FEV_1$ percent predicted (%), PEF (L/min) and PEFR (L/min), and will be summarized for each scheduled visit by treatment group for each age group and overall in the Safety Population.

Spirometry results will be presented for each subject in a data listing.

### 7.9.5. Physical Examination

Full physical examinations including height and weight are collected at Screening, Week 40 and ET visits. Abbreviated physical examinations are collected at Baseline (Day 1), all bi-weekly visits up to Week 38, Follow-up, and at unscheduled visits (if clinically indicated per the investigator's discretion).

For weight and derived BMI, observed values and change from baseline will be summarized for the Safety Population via descriptive statistics by age group, treatment group and scheduled visit.

For qualitative physical examination parameters, the normality/abnormality for each parameter at each scheduled visit will be summarized by age group, treatment group and overall using number and percent of subjects in the Safety Population

Physical examination data will be listed and any clinically significant abnormal results will be flagged using the Safety Population.

### 7.9.6. Assessment of Asthma Severity Using NHLBI

Assessment of asthma severity will be collected at Screening, Baseline (Day 1) Week 20, Week 38, ET and at unscheduled visits (if clinically indicated per the investigator's discretion).

The number and percent of subjects by NHLBI asthma classification will be presented at each time point and/or visit.

All asthma NHLBI assessment data will be listed.

# 8. Interim Analysis

## 8.1. Interim Analysis

No interim analysis is planned for this study.

## 8.2. Independent Data Monitoring Committee and Eosinophilic Esophagitis Adjudication Committee

An iDMC, composed of medical and statistical experts with experience in drug development and FA, will meet at the following intervals during the study.

- The first iDMC meeting is planned to occur either (1) after 25% of subjects are enrolled or (2) six (6) months after the first subject is enrolled, whichever occurs first.
- Subsequent iDMC meetings will be held at least every 6 months.

There are four planned iDMC meetings: one organizational meeting and 3 subsequent meetings. Additional meeting(s) could be organized on an ad hoc basis, when deemed necessary by Alladapt Immunotherapeutics, Inc. or by the iDMC members.

The iDMC will review clinical data and provide advice on the progress of the study. The iDMC, based on data review, can recommend, in its judgment, to suspend enrollment or halt the study for any substantial imbalance in AEs, apart from dosing symptoms. An unblinded statistical team will perform the analyses to maintain the blinding of the study.

Guidelines for the operation, monitoring and data output plans of the iDMC are included in a separate iDMC Charter.

An EoE Adjudication Committee, composed of allergist and gastroenterologist members with expertise in EoE, will be convened when needed to review individual cases and provide their expert input on steps to evaluate and manage the subject(s) who are initiated on the EoE evaluation, as well as to make a determination about suitability to continue on study treatment (See study protocol Section 10.4.2.2 and Section 10.4.2.3 for evaluation and management of EoE, respectively). Guidelines for the operation and monitoring plans of this committee will be included in the EoE Adjudication Committee Charter.

## 9. Changes from Analysis Planned in Protocol

Compared to the Protocol Amendment 4 (Dated: 02 September 2022), the following exploratory endpoints and analysis were added to the SAP:

- Maximum severity of allergy symptoms
- MTD for each qualifying FA; for non-qualifying reactive FA
- Proportion of subjects with their MTDs at Exit DBPCFC greater than their MTDs at Screening DBPCFC for that food in each treatment group for the following food sources: peanut, tree nut, milk, soy, wheat, sesame, fin fish, shrimp, egg.
- Use of epinephrine as a rescue medication for AESIs
- Proportion of subjects with accidental exposure, including any accidental exposure, accidental exposure requiring treatment, and accidental exposure requiring hospitalization
- Maintenance dose for study drug

## 10. Amendments to the Statistical Analysis Plan

Compared to the SAP Version 1.0 (Dated: 27 June 2022), the changes in the SAP Version 2.0 are summarized in the table below.

| Section Number and Name | Description of Change | Rationale for Change |
|---|---|---|
| 1 Introduction | • Updated reference to protocol to reflect that the SAP is based on Amendment 4 of the clinical study protocol | • To align the SAP with the protocol |
| 3.1 Overall Design | • Revised language regarding the updosing, maintenance and exit food challenge/Week 40 visit portions of the treatment period<br>• Added the protocol name of the ADP101 open-label extension study<br>• Revised language defining results of Screening DBPCFC in Figure 3 | • For clarity and consistency with the protocol |
| 6.1 General Methods<br>7.8.3.4 Biomarkers for Each Food Allergy<br>7.8.3.5 Skin-Prick Test<br>7.8.3.7 Quality of Life Assessments<br>7.9 Safety Analysis | • Revised to indicate that, in general, summary tables will be provided for pediatric subjects and for all subjects (pediatric and adult subjects, combined) and for primary and secondary endpoints summary tables for adult subjects will also be provided. | • To reduce the overall number of output generated to focus on populations and outcomes of primary interest |
| 6.2.3 Study/Treatment Period<br>6.4.3 Relationship between Analysis Visit and Study/Treatment Period | • Revised language regarding the duration of the exit food challenge/Week 40 visit portion of the treatment period | • For clarity and consistency with the protocol |
| 6.8.1 Primary Efficacy Endpoint and Analysis | • Clarified factors used for sensitivity analysis<br>• Added a section describing planned supplemental analyses using the estimand framework | • To provide clarity and to describe planned supplemental analyses which will aid in the interpretation of study results |
| 7.8.3.1 Characterizing Response in Multiple Food Allergies | • Added summaries presented by number of qualifying FAs | • To provide clarity and to describe additional planned summaries |
| 7.9.1 Adverse Events | • Added exposure-adjusted summary of treatment-emergent SAEs<br>• Modified the list of planned AE summary tables by SOC and PT | • To provide clarity around planned safety output |

| | | |
|---|---|---|
| | • Modified the list of planned AE tables summarized by study period | |
| General | • Corrected typographical errors<br>• Made minor consistency changes and clarifications throughout the SAP | • For clarity and consistency with the protocol |

## 11. Programming Specifications and Considerations

The corresponding programming specifications for variables for this SAP will be provided in a separate document.

## 12. Table, Figure, and Listing (TFL) Shells

The corresponding TFL shells for this SAP will be provided in a separate document.

## 13. References

1. Study Protocol. Version: Amendment 2., A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults (The Harmony Study)

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference on Harmonization; 1998.

3. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials; May 2021.

4. Sampson, H. A., Gerth van Wijk, R., Bindslev-Jensen, C., Sicherer, S., Teuber, S. S., Burks, A. W., et al. (2012). Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 130(6): 1260-1274.

5. Vickery, B. P., Vereda, A., Casale, T. B., Beyer, K., du Toit, G., Hourihane, J. O., et al. (2018). AR101 oral immunotherapy for peanut allergy. N Engl J Med 379(21): 1991-2001.

6. Simes, R. J. (1986). An improved Bonferroni procedure for multiple tests of significance. Biometrika 73(3): 751-754.

7. Holm, S. (1979). A Simple Sequentially Rejective Multiple Test Procedure. Scand J Stat 6(2): 65-70.

8. Chinchilli VM, Fisher L, Craig TJ. (2005) Statistical issues in clinical trials that involve the double-blind, placebo-controlled food challenge. J Allergy Clin Immunol 115:592-7.

# 14. Appendices

## Appendix 1: Schedule of Activities

| **Note: Refer to Protocol Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Treatment Period** | | | | | | | |
| **Procedure** | **Screening*** | **Day1/BL** | **Week 2–38‡ (every 2 weeks)** | **Week 40#** | **EOT** | **ET** | **UNS&** | **FU^** | **Notes** |
| Visit window | ≤ 12 weeks before Day 1 | NA | ± 4 days | -2 days to +6 weeks | Up to + 4 weeks from last Exit DBPCFC | NA | NA | ± 5 days | *Screening will be done over multiple visits.<br>‡When a subject completes updosing, every other visit can occur over the telephone.<br>#Week 40 visit can be done over multiple visits over 6 weeks to accommodate multiple Exit DBPCFCs. This period may be extended to up to 8 weeks if a subject requires > 6 food challenges.<br>&Unscheduled visit as clinically indicated.<br>^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE. |
| Informed consent/assent | X | | | | | | | | |
| Eligibility criteria | X | X | | | | | | | |
| Demography | X | | | | | | | | |
| Medical/surgical history | X | X* | | | | | | | *Update as needed. |
| Diet and food allergy status and other allergy status | X | X* | Week 38 only | | | | | | *Update as needed. |
| Assessment of asthma severity using NHLBI criteria | X | X | Week 20; Week 38 | | | X | X* | | Note: For subjects with asthma only. Assessments based on symptomatology, as clinically indicated.<br>*If indicated. |
| Concomitant medications | X | X | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | Note: Including blood pressure, heart rate, respiratory rate, temperature. |
| Full PE, including height and weight | X | | | X | | X | | | At Screening and Week 40 prior to the first DBPCFC in the series |
| Pregnancy test | Serum | Urine (U) | U (Weeks 12 and 24 only) | U | U | U | U* | | For women of childbearing potential.<br>*If indicated. |
| Hematology and chemistry | X# | | Week 38 only | | | X | X* | X | *If indicated.<br># Blood to be drawn prior to Screening DBPCFC |

| **Note: Refer to Protocol Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Treatment Period** | | | | | | | |
| **Procedure** | **Screening*** | **Day1/BL** | **Week 2–38‡ (every 2 weeks)** | **Week 40#** | **EOT** | **ET** | **UNS&** | **FU^** | **Notes** |
| Blood draw for specific IgE, IgG4, total IgE and total IgG4 | X* | | Week 20; Week 38 | | | X | | | *Blood to be drawn prior to Screening DBPCFC. |
| Skin-prick tests for 15 food sources in ADP101 | X* | | Week 38 only | | | X | | | *To be conducted prior to DBPCFC |
| AEs/allergy symptoms/EoE symptoms | X | X | X | X | X | X | X | X | AEs will be tracked from onset until the event is resolved or medically stable, or until 14 days after the subject completes the study, whichever comes first.<br>For EoE, refer to Protocol Section 10.4.2. |
| Confirm 2 EAIs available | X | X | X | X | X | X | X | X | Note: Both EAIs should be nonexpired and available for inspection at study visits prior to in-clinic updosing procedure. Provide training on EAI use as needed. |
| Reminder to subjects to avoid foods containing known food allergen(s) | X | X | X | X | X | X | X | X | |
| FAAP training | X | | Weeks 12, 24, **and** 38 | | | | | | |
| Spirometry ($FEV_1$) | X* | | | X* | | X | X# | | Note: Only for subjects aged 6 years or older<br>*Prior to initiating the series of DBPCFCs.<br>#If clinically indicated per investigator's discretion. |
| Spirometry (PEFR)+ | X | X | X# | X | | X | X# | | +For subjects with asthma aged 6 years or older only.<br>Note: To be conducted **prior** to any DBPCFC; 3 attempts, with the best value recorded. Spirometry to be performed at any time during the study if a subject's pulmonary status is in question.<br><br>#If clinically indicated per investigator's discretion. |

| **Note: Refer to Protocol Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Treatment Period** | | | | | | | |
| **Procedure** | **Screening*** | **Day1/BL** | **Week 2–38‡ (every 2 weeks)** | **Week 40#** | **EOT** | **ET** | **UNS&** | **FU^** | **Notes** |
| Peak flow meter | X* | X | X# | X* | | X | X# | X# | Note: only for subjects aged 4 to < 6 years<br>* Prior to initiating series of DBPCFCs in non-asthmatic and prior to each DBPCFC in asthmatic subjects.<br>#If clinically indicated per investigator's discretion. |
| Pulse oximetry | X+ | X | X* (updosing) | X+ | | X | | | +To be performed in all subjects as a complement to spirometry prior to each DBPCFC in the series or updosing procedure<br>*Not required at Week 38 |
| DBPCFC | X* | | | X# | | X^ | | | To be overseen by a physician or qualified clinician designee.<br>Study drug is not to be taken on the day of an Exit DBPCFC.<br>*Screening DBPCFC: refer to Figure 2.<br>#Exit DBPCFC: refer to Figure 4.<br>^ET DBPCFC: consult Study Medical Monitor |
| Dispense stool collection kit | X* | | Week 38 only | | | | | | Note: For microbiome analysis.<br>*Subjects should collect the sample prior to dosing with study drug |
| FAQLQ | X* | | Week 20 | X* | X | X | | | *Administer prior to the first Screening and Exit DBPCFC. |
| IQoL | X* | | Week 20 | X* | X | X | | | *Administer prior to the first Screening and Exit DBPCFC. |
| ACT+ or C-ACT+ | X* | | | X* | X | X | | | *Administered prior to the first Screening and Exit DBPCFC.<br>+For subjects with asthma only. |
| FAQL-PB questionnaire | X* | | Week 20 | X* | X | X | | | *Administer prior to the first Screening and Exit DBPCFC. |
| TSQM-9 | | | Week 20 | X* | X | X | | | *Administer prior to the first Exit DBPCFC. |
| Training on DISP | | X | Weeks 12, 24, **and** 38 | | | | | | |

| **Note: Refer to Protocol Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Treatment Period** | | | | | | | |
| **Procedure** | **Screening*** | **Day1/BL** | **Week 2–38‡ (every 2 weeks)** | **Week 40#** | **EOT** | **ET** | **UNS&** | **FU^** | **Notes** |
| Blood draw for exploratory biomarkers | | X | Week 20; Week 38 | | | X | | | Note: To be used to evaluate additional biomarkers including, but not limited to, PBMC, microRNA, and DNA methylation (as outlined in Protocol Section 8.4). |
| Train subject on mApp | | X | | | | | | | |
| Abbreviated PE (Section **Error! Reference source not found.**) | | X | X | | | | X* | X | Note: To be done pre-updosing.<br>* If clinically indicated.<br>At Screening and Week 40 prior to each DBPCFC in the series (except the first DBPCFC in each series) |
| Subject daily diary | | ←======= Daily completion=======→ | | | | | | | The diary is intended to capture dose compliance and dosing-related symptoms that may occur. |
| PRO for accidental exposure (when it occurs) | | ←==========→ | | | | | | | |
| Study drug administration | | ←====Oral daily dosing=====→ | | | X+ | | X* | | Note: Self-administer (at home after administration of first dose of each new dose level in the clinic)<br>Study drug is not to be taken on the day of an Exit DBPCFC.<br>+ EOT drug administration will occur as part of the Open-label extension study<br>*If needed. |
| In-clinic observation post–study drug administration | | X | X | | | | X* | | Subject to be observed for a minimum of 2 hours after initial study drug administration and after every initial updosing to a new dose level. *Refer to Protocol Section 6.5.2 for dose modifications. |
| Dispense/return study drug | | X | X | X | X* | | X# | | *Return only.<br>#If needed. |
| Telephone follow-up | | | X | X | | | | | Note: One day after each updosing visit, to inquire about allergic symptoms and promote adherence to treatment and remind subjects to complete the daily diary. |

| **Note: Refer to Protocol Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Treatment Period** | | | | | | | |
| **Procedure** | **Screening*** | **Day1/BL** | **Week 2–38‡ (every 2 weeks)** | **Week 40#** | **EOT** | **ET** | **UNS&** | **FU^** | **Notes** |
| Assess eligibility for the OLE | | | | X | | | | | Note: If not continuing to OLE, subjects will need counseling for withdrawing from study drug. |
| PEESS (pediatric) or EEsAI (adults) | | | | | | | X | | If clinically indicated in event of suspicion of EoE |

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BL = Baseline; C-ACT = Childhood Asthma Control Test; DBPCFC = double-blind, placebo-controlled food challenge; DISP = dosing instructions and symptom management plan; EAI = epinephrine autoinjector; EoE = eosinophilic esophagitis; EEsAI = Eosinophilic Esophagitis Activity Index; EOT = End of Treatment; ET = Early Termination; FAAP = Food Allergy & Anaphylaxis Emergency Care Plan; FAQL-PB = Food Allergy Quality of Life–Parental Burden; FAQLQ = Food Allergy Quality of Life Questionnaire; $FEV_1$ = forced expiratory volume in the first second; FU = follow-up visit; IgE = immunoglobulin E; IgG4 = immunoglobulin G, subclass 4; IQoL = immunotherapy-related quality of life; mApp = mobile application; NA = not applicable; NHLBI = National Heart, Lung, and Blood Institute; OLE = open-label extension; PBMC = peripheral blood mononuclear cell; PE = physical examination; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PEFR = peak expiratory flow rate; PFM = peak flow meter; PRO = patient-reported outcome; TSQM-9 = 9-Item Treatment Satisfaction Questionnaire for Medication; UNS = unscheduled visit.

## Appendix 2: Laboratory Assessments

| Hematology | |
|---|---|
| White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) | Red blood cell (RBC) count with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) |
| Hemoglobin | Hematocrit |
| Platelet count | |
| **Clinical Chemistry** | |
| Alanine aminotransferase (ALT) | Aspartate aminotransferase (AST) |
| Alkaline phosphatase | Gamma-glutamyl transferase (GGT) |
| Total and direct bilirubin (fractionated) | Albumin |
| Calcium | Blood urea nitrogen (BUN) |
| Sodium | Creatinine |
| Chloride | Potassium |
| Glucose (nonfasting) | Lactic dehydrogenase (LDH) |
| Uric acid | Magnesium |
| Total protein | Phosphorus |
| Bicarbonate | |
| **Other Laboratory Assessments** | |
| Human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) | |

Note: Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Revision History**

| Version | Date | Comments |
|---|---|---|
| 0.1 (Draft) | 30 Jul 2021 | First draft |
| 0.2 (Draft) | 09 Aug 2021 | Updated per sponsor's comments |
| 0.3 (Draft) | 16 Aug 2021 | Updated per sponsor's comments |
| 0.4 (Draft) | 27 Aug 2021 | Updated per sponsor's comments |
| 0.5 (Draft) | 22 Sep 2021 | Updated per sponsor's comments |
| 0.6 (Draft) | 15 Oct 2021 | Updated per sponsor's comments |
| 0.7 (Draft) | 27 Oct 2021 | Updated per sponsor's comments |
| 0.8 (Draft) | 04 Apr 2022 | Updated per sponsor's comments |
| 0.9 (Draft) | 28 Apr 2022 | Updated per sponsor's comments |
| 0.10 (Draft) | 07 June 2022 | Updated per sponsor's comments |
| 0.11 (Draft) | 15 Jun 2022 | Updated per sponsor's comments |
| 1.0 (Final) | 27 Jun 2022 | Finalization |
| 1.1 (Final) | 17 Oct 2022 | Amended per the protocol amendment and sponsor's comments |
| 2.0 (Amendment 1) | 19 Oct 2022 | Finalization of Amendment 1 |