CLINICAL STUDY PROTOCOL

Protocol Title:	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)
Protocol Number:	ADP101-MA-01
Study Drug:	ADP101
Study Phase:	Phase 1/2
Clinical Site(s)	Approximately 20 sites in the United States
Sponsor Name:	Alladapt Immunotherapeutics, Inc.
Sponsor Address:	650 Live Oak Ave., Suite 200 Menlo Park, CA 94025
Regulatory Agency Identifier No(s):	IND: 26082
Version:	Amendment 4
Final Date:	02 September 2022

[redacted]

SPONSOR SIGNATORY

Protocol Title	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)
Protocol Number	ADP101-MA-01
Version	Amendment 4

I have reviewed and approve the use of this protocol.

Sponsor Representative:

[redacted]

Date

Study Medical Monitor name and contact information are provided below:

[redacted]

INVESTIGATOR AGREEMENT

ADP101-MA-01 Protocol: 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)

I have read this protocol and agree to conduct this study in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements, and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Alladapt Immunotherapeutics, Inc.

_____

Signature

_____ _____

Name of Investigator Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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)

Study Rationale

ADP101 is an oral formulation mixture of 15 individual food sources containing allergenic proteins (i.e., almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat) that are responsible for approximately 90% of food allergies (FAs) in the United States. ADP101 is being developed as an oral immunotherapy (OIT) for the mitigation of allergic reactions, including anaphylaxis, that may occur following accidental exposure to the above foods in children and adults aged ≥ 4 to ≤ 55 years.

Objectives and Endpoints (Primary and Secondary Only)

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ADP101 as assessed by an increased threshold for clinical reactivity to at least one Qualifying Food (see Figure 3) for which the eliciting dose was ≤ 100 mg at Screening	• Proportion of subjects who tolerate the 600-mg level of a single Qualifying Food without dose-limiting symptoms at the Exit double-blind, placebo-controlled food challenge (DBPCFC)
Secondary	
• To evaluate the efficacy of ADP101 as assessed by an increased threshold to one or more Qualifying Food (for which the eliciting dose was ≤ 100 mg at Screening)	• 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
Safety	
• To evaluate the safety and tolerability of ADP101 in subjects with FA	• Incidence of adverse events (AEs) and serious adverse events (SAEs)

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).

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 updosing and maintenance portions.

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 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 Foods, defined as either a) Qualifying Foods that elicit a reaction at ≤ 100 mg during the Screening DBPCFC, or b) Non-qualifying Foods that elicit a reaction at > 100 mg but ≤ 1000 mg during the Screening DBPCFC
2. Non-reactive Foods, 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 Foods 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.

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 attempts, this will trigger randomization of another subject.

Updosing portion of the Treatment Period: 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 updosing (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 highest tolerated dose.

Maintenance portion of the Treatment Period: Once the appropriate target dose (or highest tolerated 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.

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) 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 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 Non-reactive Foods at Screening will be reevaluated to assess for potential new FA development 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).

After the final Exit DBPCFC, all subjects will continue to receive study drug at their treatment 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 OLE (under a separate protocol [ADP101-MA-02] and informed consent/assent).

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 (SoA) in Section 1.3. 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).

Number of Subjects, Intervention Groups, and Duration

Intervention Groups

Table 1: Treatment Arms

Treatment Arm	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	Up to 4
2	ADP101	High-dose	4500 mg/day (300 mg per food source)	24	20	Up to 4
3	Placebo	Low-dose	(Content volume-matched)	12	10	Up to 2
4	Placebo	High-dose	(Content volume-matched)	12	10	Up to 2

Study Duration

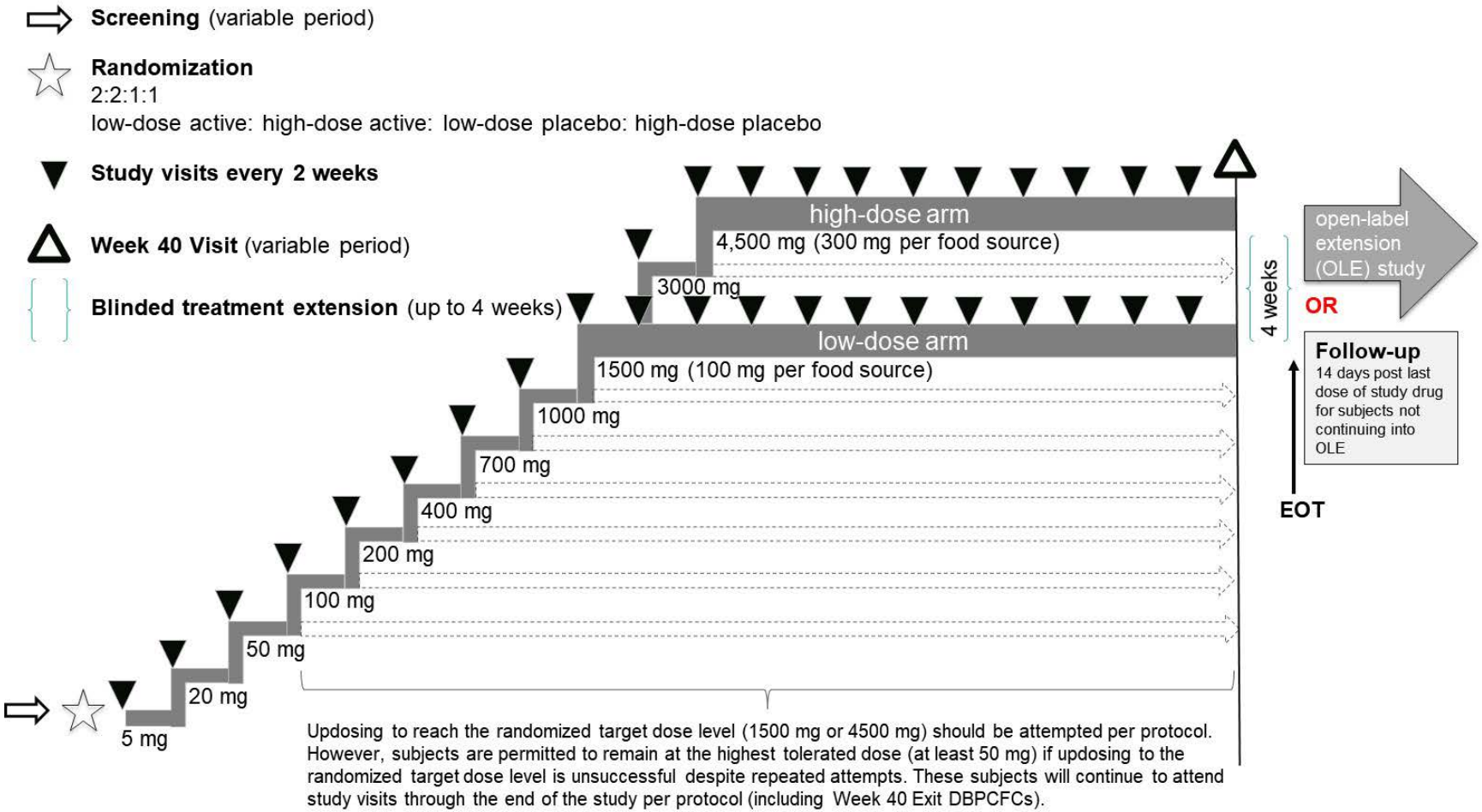
For each subject, the study is expected to last as follows:

Screening period:	Up to 12 weeks
Treatment period:	Up to 50 weeks (includes 40 weeks of treatment plus up to 6 weeks for Exit DBPCFCs [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 drug treatment through EOT); the treatment period will consist of an updosing portion and a maintenance portion, which will be variable per subject.
Follow-up period:	Up to 14 days from EOT

Independent Data Monitoring Committee (iDMC): Yes

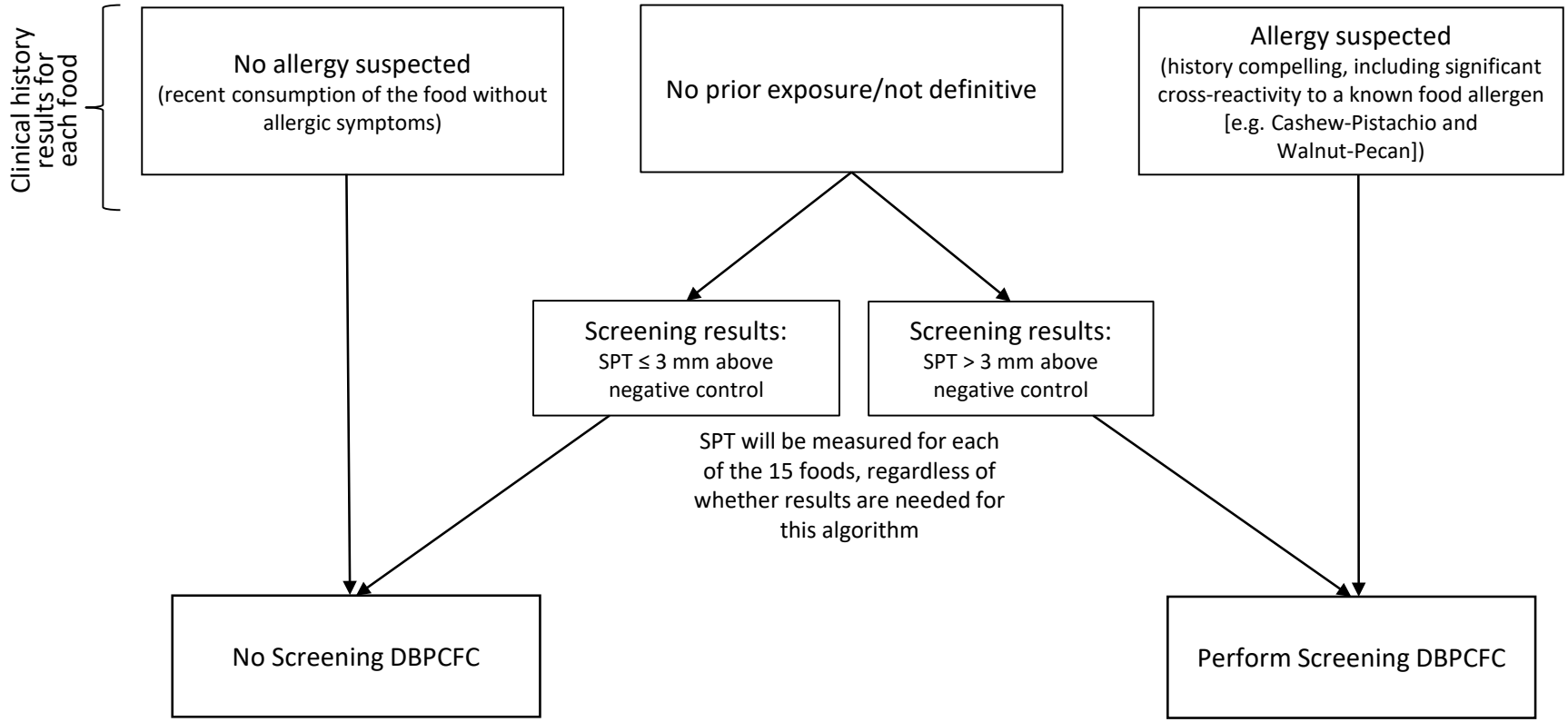
1.2. Study Schema

Figure 1: Study Schema



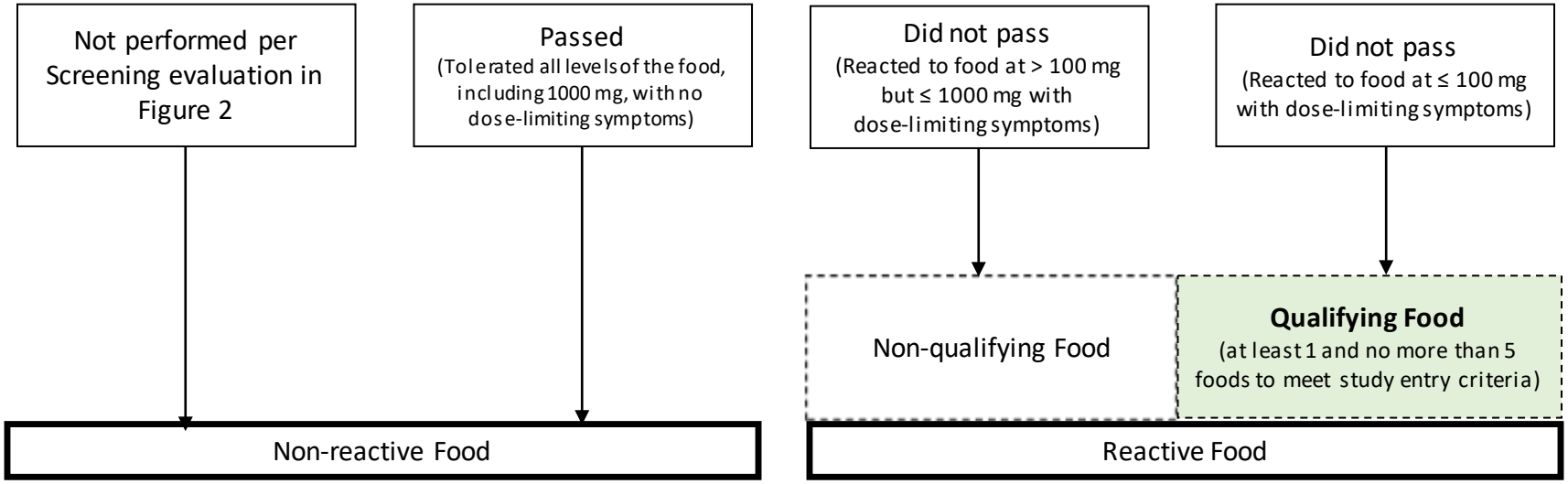
Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge; EOT = End of Treatment; OLE = open-label extension.

Figure 2: Screening Evaluation to Determine Individual Food DBPCFC Testing



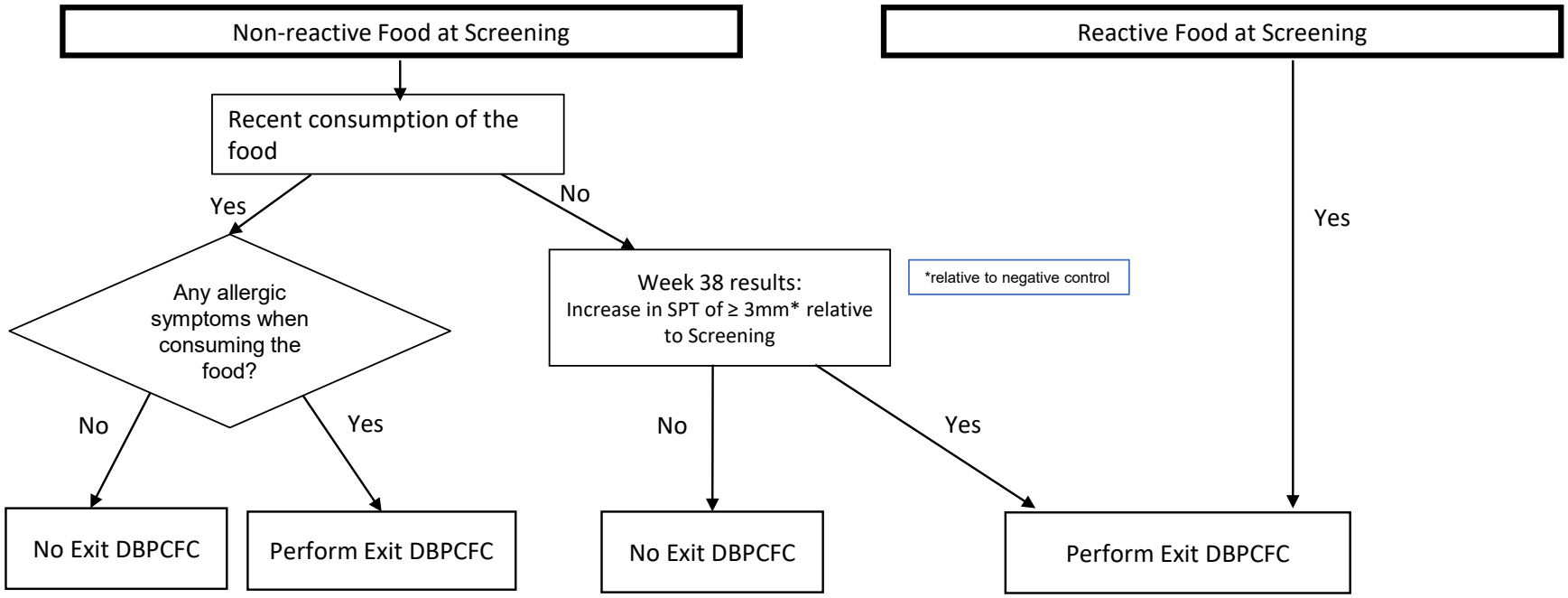
Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge; SPT = skin-prick test.

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) ≥ 3 mm.

1.3. Schedule of Activities

Table 2: Schedule of Activities

Note: Refer to Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.									
		Treatment Period							Notes
Procedure	**Screening***	**Day1/BL**	**Week 2–38‡ (every 2 weeks)**	**Week 40#**	**EOT**	**ET**	**UNS&**	**FU^**	*Screening will be done over multiple visits. ‡When a subject completes updosing, every other visit can occur over the telephone. #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. &Unscheduled visit as clinically indicated. ^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE.
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	
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. *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. *If indicated.
Hematology and chemistry	X#		Week 38 only			X	X*	X	*If indicated. # Blood to be drawn prior to Screening DBPCFC
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.

Note: Refer to Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.									
		Treatment Period							**Notes**
Procedure	**Screening***	**Day1/BL**	**Week 2–38‡ (every 2 weeks)**	**Week 40#**	**EOT**	**ET**	**UNS&**	**FU^**	*Screening will be done over multiple visits. ‡When a subject completes updosing, every other visit can occur over the telephone. #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. &Unscheduled visit as clinically indicated. ^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE.
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	
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. For EoE, refer to 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 *Prior to initiating the series of DBPCFCs. #If clinically indicated per investigator's discretion.

Note: Refer to Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.									
		Treatment Period							**Notes**
Procedure	**Screening***	**Day1/BL**	**Week 2–38‡ (every 2 weeks)**	**Week 40#**	**EOT**	**ET**	**UNS&**	**FU^**	*Screening will be done over multiple visits. ‡When a subject completes updosing, every other visit can occur over the telephone. #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. &Unscheduled visit as clinically indicated. ^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE.
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	
Spirometry (PEFR)+	X	X	X#	X		X	X#		+For subjects with asthma aged 6 years or older only. 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. #If clinically indicated per investigator's discretion.
Peak flow meter	X*	X	X#	X*		X	X#	X#	Note: only for subjects aged 4 to < 6 years * Prior to initiating series of DBPCFCs in non-asthmatic and prior to each DBPCFC in asthmatic subjects. #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 *Not required at Week 38
DBPCFC	X*			X#		X^			To be overseen by a physician or qualified clinician designee. Study drug is not to be taken on the day of an Exit DBPCFC. *Screening DBPCFC: refer to Figure 2. #Exit DBPCFC: refer to Figure 4. ^ET DBPCFC: consult Study Medical Monitor

Note: Refer to Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.									
		Treatment Period							**Notes**
Procedure	**Screening***	**Day1/BL**	**Week 2–38‡ (every 2 weeks)**	**Week 40#**	**EOT**	**ET**	**UNS&**	**FU^**	*Screening will be done over multiple visits. ‡When a subject completes updosing, every other visit can occur over the telephone. #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. &Unscheduled visit as clinically indicated. ^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE.
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	
Dispense stool collection kit	X*		Week 38 only						Note: For microbiome analysis. *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. +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						
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 Section 8.4).
Train subject on mApp		X							
Abbreviated PE (Section 8.2.1)		X	X				X*	X	Note: To be done pre-updosing. * If clinically indicated. 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.

Note: Refer to Appendix 6 (Section 10.6) for guidance regarding study assessments and procedures during public health emergency.									
		Treatment Period							**Notes**
Procedure	**Screening***	**Day1/BL**	**Week 2–38‡ (every 2 weeks)**	**Week 40#**	**EOT**	**ET**	**UNS&**	**FU^**	*Screening will be done over multiple visits. ‡When a subject completes updosing, every other visit can occur over the telephone. #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. &Unscheduled visit as clinically indicated. ^Follow-up visit will be 14 days post-EOT, only for subjects who will not continue to the OLE.
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	
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). Study drug is not to be taken on the day of an Exit DBPCFC. + EOT drug administration will occur as part of the Open-label extension study *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 Section 6.5.2 for dose modifications.
Dispense/return study drug		X	X	X	X*		X#		*Return only. #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.
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.

2. INTRODUCTION

ADP101 is an oral formulation mixture of 15 individual food sources containing allergenic proteins (i.e., almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat; refer to the Investigator's Brochure [IB] for details on each ingredient within ADP101) that are responsible for approximately 90% of food allergies (FAs) in the United States (Boyce, 2010; FDA, 2017; Gupta, 2019). ADP101 is being developed as an oral immunotherapy (OIT) for the treatment of FA triggered by 1 or more of the food sources found in ADP101 in children and adults.

2.1. Study Rationale and Hypothesis

The goal of OIT for FA is to induce a state of clinically meaningful desensitization to food proteins, defined as the absence of moderate or severe allergic reaction following ingestion of small, but potentially dangerous, amounts of food protein. For example, in peanut-allergic subjects, increasing the baseline threshold before immunotherapy from 100 mg or less of peanut protein to 300 mg or more of peanut protein post-immunotherapy reduces the risk of experiencing an allergic reaction by more than 95% for 4 common food product categories that may contain trace levels of peanut residue. This level of risk reduction is highly clinically relevant. Further increase in the threshold to 1000 mg has an additional quantitative benefit in risk reduction (Baumert, 2018; Chinthrajah, 2019).

The existing clinical data from the published literature on single OIT for FAs (Staden, 2007; Varshney, 2011; Burks, 2012; Anagnostou, 2014; Caminiti, 2015; Escudero, 2015; Tang, 2015; Feuille, 2016; Bird, 2018; Elizur, 2019) and of multiple-allergen oral immunotherapy (mOIT) (Begin, 2014a; Begin, 2014b; Andorf, 2018; Andorf, 2019; Chinthrajah, 2019) form the basis for supporting further development of ADP101 as an OIT for the mitigation of allergic reactions, including anaphylaxis, that may occur following accidental exposure to almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat in children and adults aged ≥ 4 to ≤ 55 years.

2.2. Background

FA is a common and serious condition that affects children and adults and is commonly associated with severe reactions, including life-threatening anaphylaxis. Allergy to peanuts, tree nuts, fish, or shellfish is most commonly associated with fatal and near-fatal food-induced anaphylaxis (Jones, 2017a). Published reports suggest that the prevalence of FA has been rising, and it is now estimated to affect up to 10% of the worldwide population (Branum, 2008; Sicherer, 2014; Gupta, 2018; Gupta, 2019).

Multi-allergic subjects are becoming increasingly common in the United States. Recent data show that approximately 30% to 60% of food-allergic patients were allergic to multiple foods (Wang, 2010; Andorf, 2017; Gupta, 2018; Vickery, 2018; Gupta, 2019; Brough, 2020). In the Phase 3 PALISADE (Peanut Allergy Oral Immunotherapy) study by Aimmune Therapeutics, approximately two-thirds of the peanut-allergic subjects enrolled in the study were allergic to 1 or more foods in addition to the peanut (Vickery, 2018). In nationwide epidemiological surveys of US adults and children, subjects who are reactive to foods other than peanuts also show high

rates of allergy to multiple foods (Gupta, 2018; Gupta, 2019). Additionally, a similar ratio of multi-allergic patients was noted in a separate Phase 3 study reported in the PALFORZIA® label (PALFORZIA Package Insert, 2020). In both adults and children, approximately 90% or more of subjects allergic to 1 tree nut (e.g., walnuts, almonds, hazelnuts, pecans, cashews, or pistachios) were allergic to multiple foods, and more than 60% of subjects with milk, egg, wheat, soy, finfish, shrimp, or peanut allergies were allergic to multiple foods. In a separate study, about one-half of multi-allergic subjects were found to have unique combinations of FAs (Andorf, 2017). Allergies to multiple foods increase the risk of anaphylaxis (due to accidental ingestion), increase anxiety, and worsen the disabling nature of FA for patients and their families, with significant impact on quality of life. Children with multiple FAs are also more likely to experience an allergic reaction (0.7 to 3.4 reactions per year) compared with children with single FA (0.2 reactions per year) (Kapoor, 2004).

The current options in the management of the majority of foods that trigger FA include OIT for specific foods (e.g., PALFORZIA for peanut allergy), dietary avoidance of the allergenic food, and education of the patient/family on acute management of an allergic reaction. The burden of avoidance and constant fear of accidental exposure can negatively affect the health-related quality of life (HRQoL) of both patients and their families (Shaker, 2017; Howe, 2019). Despite efforts toward strict food allergen avoidance, accidental exposure continues to be a major concern in FA because allergic responses can be triggered after ingestion of milligram quantities of food allergen protein.

An approach that has shown consistently promising results is allergen-specific immunotherapy, a therapy that entails administration of increasing amounts of an allergen to individuals with immunoglobulin E (IgE)–mediated FA to raise the threshold and decrease the severity of allergic responses to the allergenic food. These allergen-based immunotherapies include sublingual immunotherapy, epicutaneous immunotherapy, and OIT.

OIT for FA using individual food allergens such as peanuts, milk, and eggs has been widely studied in recent years and has demonstrated that OIT can effectively desensitize a majority of patients to a food allergen (Varshney, 2011; Nurmatov, 2014; Narisety, 2015; Feuille, 2016; Vickery, 2018). Offending foods to which an individual is allergic are slowly reintroduced under professional clinical supervision to gradually desensitize the patient's immune system. More recently, administration of mOIT for multiple food sources simultaneously suggests the potential for parallel desensitization to multiple foods within the same overall timeframe (Begin, 2014a; Begin, 2014b; Andorf, 2018).

A Phase 1 study (Begin, 2014b) of mOIT demonstrated that individuals allergic to multiple foods can be safely desensitized to up to 5 foods simultaneously, and that it is possible and feasible to achieve desensitization simultaneously, rather than by performing single OIT in a sequence for individuals, a process that could take many years for individuals who are sensitized to multiple foods. Furthermore, the rate of reactions in the mOIT group was acceptable and similar to that of the group that received peanut OIT alone, supporting the approach of using mOIT in subjects allergic to multiple foods.

As several studies reported the effectiveness of desensitization to multiple foods simultaneously (Begin, 2014a; Begin, 2014b; Andorf, 2018), it is expected that the combination of 15 food sources in ADP101 will be effective for each FA in a way that may be comparable to results seen in single OIT. It is anticipated that, in this study, subjects with double-blind, placebo-controlled

food challenge (DBPCFC)–confirmed qualifying FA to at least 1 and no more than 5 food sources in ADP101 will be gradually desensitized to these Reactive Foods through controlled exposure and updosing. It is also anticipated that the consumption of Non-reactive Foods (see Section 4.1) in ADP101 will not lead to development of new clinical FA. This expectation is based upon clinical studies such as the LEAP (Learning Early about Peanut Allergy) study (Du Toit, 2018), which demonstrated that early introduction and regular consumption of peanuts significantly decreased the frequency of peanut allergy among children with egg allergy and/or severe eczema. In a separate peanut OIT study, sensitization analyzed by IgE profiles using microarrays showed no new sensitization to cross-reactive allergens. (Uotila, 2017). While no new sensitization events are expected when dosing with ADP101, this expectation will be evaluated over the course of this Phase 1/2 study. Specifically, at the end of the study period, subjects will be assessed for any new clinical allergy symptoms (as assessed by clinical status) and/or skin-prick test (SPT) changes (as per Figure 4) with targeted DBPCFC to assess if there is new reactivity to foods classified as Non-reactive Foods at Screening.

2.3. Benefit and Risk Analysis

2.3.1. Benefit Assessment

The clinically relevant goal of OIT is to induce a meaningful state of desensitization (or increased tolerance) for food allergens in individuals with FA, thereby reducing the risk of serious life-threatening anaphylaxis due to accidental exposure. Numerous OIT studies performed in subjects with FA that used procedures and dosing regimens similar to those proposed for the current study have demonstrated a meaningful level of desensitization to food allergens in a majority of study subjects (Begin, 2014a; Begin, 2014b; Andorf, 2018). mOIT has demonstrated the potential to effectively desensitize subjects to multiple foods (simultaneously) with a rate of reaction comparable to those observed among subjects undergoing desensitization to a single food (Begin, 2014b). Additionally, long-term follow-up studies of OIT in subjects support feasibility of sustained desensitization through long-term maintenance dosing (Andorf, 2018).

More recently, the PALISADE study demonstrated clinically meaningful efficacy of OIT using PALFORZIA, with subjects showing increased tolerance to peanut powder compared with those receiving placebo at the Exit DBPCFC. The study demonstrated an overall treatment difference of 63.2% at the 600-mg level compared with placebo, as well as an increased tolerance at both lower and higher challenge doses to peanut protein at an Exit DBPCFC (68.5% at 300 mg and 47.8% at 1000 mg). In addition, the PALISADE study demonstrated a decrease in overall severity of symptoms during the Exit DBPCFC in PALFORZIA-treated subjects compared with placebo-treated subjects (Vickery, 2018; Hise, 2020).

In this Phase 1/2 study, both the safety and efficacy of ADP101 will be evaluated in subjects with a demonstrated allergy to multiple qualifying food sources. The study will also explore the potential benefit of this treatment in lessening the burden of FA by identifying quality-of-life changes for those undergoing OIT for allergy to single and multiple foods.

2.3.2. Risk Assessment

In this ongoing study, as of March 2, 2022, study drug (ADP101 or placebo) generally has been well tolerated based on a review of blinded exposure (of at least 159 days) and safety data from 73 subjects (61 children and 12 adults) who were enrolled and randomized (blinded treatment ADP101 or placebo).

While this study represents ADP101's first in-human study, the food sources that comprise the 15 food components used in formulating ADP101 have been used in previous OIT clinical studies, case studies, and clinical settings of customized desensitization protocols (Varshney, 2011; Begin, 2014a; Begin, 2014b; Narisety, 2015; Andorf, 2018). Previous studies have characterized the risks associated with OIT and mOIT, demonstrating the need for a plan for the mitigation of risks associated with OIT and mOIT.

These studies have reported a variety of symptoms associated with OIT for FA ranging from mild allergic reactions to more serious, potentially life-threatening clinical manifestations, including anaphylaxis. Systemic allergic reactions typically seen across OIT desensitization protocols may include (but are not limited to) rash, wheezing, rhinorrhea, sneezing, itching, abdominal pain, nausea, vomiting, and diarrhea. The symptoms listed in the PALFORZIA package insert are similar to the above-mentioned symptoms (PALFORZIA Package Insert, 2020). OIT studies for FA have reported systemic allergic reactions (9.4% and 8.7% for active drug compared with 3.8% and 1.7% for placebo during initial dose escalation/updosing and maintenance, respectively, in PALFORZIA pediatric clinical studies), systemic allergic reactions requiring epinephrine administration (7.7% for active drug vs. 3.4% for placebo during PALFORZIA maintenance period), and the potential for eosinophilic esophagitis (EoE) (12 subjects treated with PALFORZIA in the entire clinical development program) in subjects (Ibanez, 2015; Gomez Torrijos, 2017; Fauquert, 2018; Hise, 2020; PALFORZIA Package Insert, 2020).

In considering the identified risks, this study includes key steps aimed at mitigating risks for participants. Subjects should document any symptoms related to at-home dosing in their electronic daily diary, which will prompt follow-up from the sites, which, in turn, will work closely with subjects for symptom management while in the study. Recognizing the potential for systemic allergic reactions requiring epinephrine, sites will ensure that subjects have readily accessible 2 nonexpired epinephrine autoinjector (EAI) devices at all times during the study. Subjects and/or their caregivers will be trained on the appropriate use of the EAI at the start of the study and periodically throughout. They will also be given the Food Allergy & Anaphylaxis Emergency Care Plan (FAAP) (and revised anaphylaxis management algorithm during public health emergencies) for reference to manage symptoms of accidental exposure, as well as the dosing instructions and symptom management plan (DISP; in Study Reference Manual).

While the incidence of EoE remains low in OIT studies and in the IgE-mediated FA patient population, subjects with a history of EoE will be excluded from participation, and investigators should be vigilant for symptoms indicative of potential EoE development in subjects, with follow-up steps to evaluate and manage patients with potential EoE as outlined in Section 10.4.2 of the protocol. This study will also aim to mitigate risk with an EoE adjudication committee to help ensure proper follow-up for subjects suspected to have EoE-related symptoms (more information can be found in Section 10.4.2).

Based upon the nature of this treatment approach, some level of allergic symptoms should be expected when exposing subjects to IgE-mediated allergens confirmed on entry DBPCFC. To help mitigate this risk, subjects with a history of severe or life-threatening episode(s) of anaphylaxis or anaphylactic shock within 60 days of the first Screening DBPCFC and subjects with a history of EoE are excluded from entering the study, and, during the study, all subjects will be carefully monitored for systemic allergic reactions, anaphylaxis, and potential EoE. Subjects with severe asthma or subjects with uncontrolled mild to moderate asthma are excluded from entering this study and all asthma subjects should be closely monitored throughout the study for any changes related to control of their asthma. Further details on the diagnosis and management of these events if encountered during study are further described in Section 10.4.1 (anaphylaxis) and Section 10.4.2 (EoE).

2.3.3. Overall Benefit: Risk Conclusion

Given the potential benefit of ADP101 as a new alternative for desensitization to mitigate the risk of life-threatening anaphylaxis when exposed to multiple offending food sources and the potential risks of ADP101 (with risk mitigation plan), the benefit-vs.-risk ratio for ADP101 is considered favorable.

The long-term and consistent clinical experience with OIT across food sources to increase the reactivity threshold in a majority of patients both provides the rationale for conducting this study and defines the potential benefit that subjects might receive from participating. This is the first clinical study with ADP101, and clinical studies of ADP101 are needed to test whether the benefit demonstrated in other OIT programs is observed with ADP101. Clinical studies will also evaluate the safety/tolerability considerations. Strict avoidance of the allergic foods will be important since clinical benefit for ADP101 has not been established and not all subjects enrolled will receive active drug.

Safety measures are included in this clinical study to monitor and protect subjects participating in the Harmony Study. These include low and slow updosing of ADP101 (with in-clinic monitoring); daily symptom collection (via daily diary); flexibility to plateau at the highest tolerated dose, as well as downdose if needed (based upon subject tolerance); subject reminder to avoid foods containing known food allergen(s); training on the DISP, with regular retraining throughout the study; and sites ensuring access to nonexpired EAI.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ADP101 as assessed by an increased threshold for clinical reactivity to at least one Qualifying Food (see Figure 3) for which the eliciting dose was ≤ 100 mg at Screening	• Proportion of subjects who tolerate the 600-mg level of a single Qualifying Food without dose-limiting symptoms at the Exit DBPCFC
Secondary	
• 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)	• 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
Safety	
• To evaluate the safety and tolerability of ADP101 in subjects with FA	• Incidence of adverse events (AEs) and serious adverse events (SAEs)
Exploratory	
• To evaluate whether Non-qualifying Reactive Foods (eliciting dose > 100 mg) respond to treatment with ADP101 • To evaluate impact of treatment on changes in FA-associated biomarkers	• Change from baseline in eliciting dose of individual Reactive Food at the Exit DBPCFC without dose-limiting symptoms • Changes from baseline in biomarkers, including, but not limited to, specific immunoglobulin E (sIgE), of all foods contained in ADP101 • Change from baseline in SPT for all foods contained in ADP101

Objectives	Endpoints
• 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	• 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
• To evaluate the development of confirmed new FAs to Non-reactive Foods contained in ADP101	• Proportion of subjects taking ADP101 vs. placebo who develop confirmed new FAs to previously Non-reactive Foods at Screening (see Section 4.1) as demonstrated by the Exit DBPCFC
• To explore additional safety endpoints	• 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 (FEV_1)/peak expiratory flow rate (PEFR) • Frequency of allergic reaction AEs during treatment normalized for duration of treatment

4. OVERALL STUDY DESIGN

4.1. Study 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).

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 updosing and maintenance portions.

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 DBPCFC testing as described in Figure 2 and Figure 3. Briefly, clinical FA history and 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 Foods, defined as either a) Qualifying Foods that elicit a reaction at ≤ 100 mg during the Screening DBPCFC, or b) Non-qualifying Foods that elicit a reaction at > 100 mg but ≤ 1000 mg during the Screening DBPCFC
2. Non-reactive Foods, 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 Foods 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.

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.

Updosing portion of the Treatment Period: 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 updosing (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 highest tolerated dose.

Maintenance portion of the Treatment Period: Once the appropriate target dose (or highest tolerated 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.

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) 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 Non-reactive Foods at Screening will be reevaluated to assess for potential new FA development during the treatment period. Each Non-reactive Foods 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).

After the final Exit DBPCFC, all subjects will continue to receive study drug at their treatment 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 OLE (under a separate protocol and informed consent/assent).

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 (SoA) in Section 1.3. 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).

The study will be monitored by an independent data monitoring committee (iDMC) as described in Section 9.6.

4.2. Scientific Rationale for Study Design

This study will evaluate the efficacy and safety of updosing ADP101 in the target population (children and adults with FAs) in a randomized, double-blind, placebo-controlled study design. The study will allow assessment of the optimal dose (low- and high-dose regimen). The total duration of treatment will be up to 50 weeks: 40 weeks during the Treatment Period plus up to 6 weeks for the Exit DBPCFCs and up to 4 additional weeks of blinded treatment through EOT for subjects rolling into the OLE.

A DBPCFC is used to ascertain the food-allergic status of a subject and is the gold standard diagnostic test for FA. Other diagnostic markers commonly used (e.g., SPTs and measurements of food-specific IgE levels) have high sensitivity, poor specificity, and no universally accepted established cutoffs, and are therefore not adequate as standalone assessments to make the diagnosis. Determination of new FA to Non-reactive Foods in response to regular consumption of ADP101 is an important goal for the study, and development of any new clinical allergy as assessed by clinical history at the end of the study will be evaluated by DBPCFC. Changes in the IgE sensitization to all 15 foods will be evaluated by measuring specific IgE and immunoglobulin G, subclass 4 (IgG4), during the study at 3 time points (Screening, Week 20, and Week 38).

All subjects enrolled must have dose-limiting symptoms, in accordance with consensus guidelines (Sampson, 2012), 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. It is expected that the threshold of ≤ 100 mg during the DBPCFC will help identify the more sensitive food-allergic subjects, especially for peanuts, milk, eggs, and hazelnuts (Remington, 2013; Allen, 2014). The requirement for reactivity at or below the 100-mg level at study entry also ensures that all subjects have a chance to achieve a maintenance dose of study drug at or above their eliciting dose for the food. This approach is consistent with precedent studies in this area (Bird, 2018; Vickery, 2018).

Subjects who comply with dosing procedures throughout the treatment period and tolerate a dose of 50 mg or higher for at least 2 weeks by Week 40 will undergo an Exit DBPCFC with the Reactive Foods and selected Non-Reactive Foods (if the prespecified criteria are met during the study; see Section 8.1.1).

4.2.1. Study Population Rationale

This study will focus on the age group most at risk from accidental exposure to food allergens (pediatric subjects ≥ 4 to < 18 years of age) (Cherkaoui, 2015; Coffman, 2015), while allowing for older subjects (≥ 18 to ≤ 55 years old) who are motivated to seek desensitization to be included as an exploratory population. While the efficacy endpoint will be analyzed in the pediatric population, safety and efficacy data will be collected and explored in the adult population, given the prevalence of adult subjects with FAs and the different profile of allergies seen specifically; evidence suggests that certain FAs (e.g., shellfish and finfish) may be more likely than others to develop during adulthood (Gupta, 2019).

The lower age limit of 4 years was selected based on epidemiologic child-developmental considerations related to feeding behavior (Farrow, 2012), as well as practical clinical study execution considerations and safety. The upper age limit of 55 years was selected to reduce the chance of enrolling subjects with clinically significant heart disease (Mozaffarian, 2015) who could be at increased risk of serious side effects from the use of epinephrine if needed to treat anaphylaxis. This is particularly relevant in the clinical study setting, in which the potential risk of anaphylaxis and/or epinephrine use may be increased due to both study drug and study procedures (e.g., the requirement for a repeated DBPCFC).

The emphasis on the pediatric subject population is also predicated on results from the PALISADE study (Vickery, 2018), in which the efficacy of AR101 was only demonstrated in subjects under 18 years of age and did not reach significance in subjects 18 to 55 years old, in part due to a high dropout rate in the adult population.

4.2.2. Rationale for Multiple Food Sources in ADP101

The rationale for including multiple food sources is to enable simultaneous treatment of 1 or more of the common causes of FAs with a single product. This approach is taken to expand treatment options for individuals with FA, both to address subjects with a single allergy to any of the 15 food sources and to enable desensitization to multiple foods simultaneously for subjects allergic to multiple foods. Recent data show that approximately 30% to 60% of food-allergic subjects are allergic to multiple foods (Brough, 2020). In Aimmune Therapeutics' Phase 3 PALISADE study, approximately two-thirds of the peanut-allergic subjects enrolled in the study were allergic to 1 or more foods in addition to peanuts (Vickery, 2018). Subjects with allergies to foods other than peanuts also showed high rates of multi-allergy in recent comprehensive nationwide surveys of US adults and children (Gupta, 2018; Gupta, 2019). Approximately 90% or more of subjects allergic to 1 tree nut (e.g., walnuts, almonds, hazelnuts, pecans, cashews, or pistachios) were allergic to multiple foods, and more than 60% of both adult and pediatric subjects with milk, egg, wheat, soy, finfish, shrimp, or peanut allergies were allergic to multiple foods. A study by Andorf et al. found that nearly one-half of multi-allergic subjects have unique combinations of FAs, making a potential product such as ADP101 a useful approach to address FAs in a broad range of subjects (Andorf, 2017). Regarding safety of treating multiple FAs simultaneously, studies have demonstrated similar rates of reaction per dose between multi- and single-OIT groups, with most reactions being mild for both groups (Begin, 2014b).

4.2.2.1. Considerations for Cross-reactivity

Clinically, it has been well recognized that certain FA occurs concurrently. For example, studies have indicated that individuals with shrimp allergy are often allergic to other shellfish. Among tree nuts, allergies to pistachios have been found to be more common in individuals with cashew allergy and individuals with walnut allergy are often allergic to pecans, and vice versa in both cases. In a study by Brough that used DBPCFC, a high correlation was seen between cashew and pistachio, as well as walnut and pecan allergy (Brough, 2020). In a study by Andorf, in a cohort of subjects with multiple FA, all subjects who were allergic to pecans (29 subjects) were also allergic to walnuts; moreover, only 3 of 32 walnut-allergic subjects (9%) tolerated pecans (Andorf, 2017). Similarly, in this cohort, all of the subjects with allergy to pistachios were DBPCFC-positive against cashews. In a large cohort of subjects with FA, a high correlation between sIgE levels has also been reported between these 2 pairs (walnuts and pecans [Spearman's rank correlation coefficient (r_s) 0.96] and cashews and pistachios [r_s 0.95]), suggesting significant serologic cross-reactivity between these pairs of nuts (Maloney, 2008). The co-occurrence of pistachio and cashew allergy has also been reported by many other studies (Noorbakhsh, 2011; Savvatianos, 2015; Uotila, 2016). Given a very high correlation of clinical co-occurrence and sIgE level correlations for these 2 pairs, a subject who reports allergy to any one of a pair of tree nuts (i.e., cashew-pistachio, or walnut-pecan) will undergo a DBPCFC to the corresponding other food in the pair (Figure 2).

4.3. Justification for Dose and Dose Regimen

The doses of ADP101 are formulated to ensure that each food source has equal parts by protein percentage in ADP101. The active study drug, ADP101, is a mixture of 15 food sources in the form of powder that are formulated with excipients into premeasured doses.

Two dosing regimens will be tested with treatment maintenance dose levels of 1500 mg (low-dose regimen) and 4500 mg (high-dose regimen) of study drug. The target daily dose of 1500 mg (100 mg/food source) will deliver 100 to 500 mg of qualifying allergenic food source in the case of subjects with 1 to 5 FAs at baseline, respectively. The 4500-mg (300 mg/food source) target daily dose will deliver between 300 and 1500 mg of allergenic food sources for the same range of qualifying FAs at baseline. The low-dose regimen of 1500 mg total protein was selected based upon the potential for synergy across multiple food sources (in vitro data on file), as well as recently emerging data that lower dose levels may be efficacious. Specifically, a recent publication from Blumchen et al. showed that 125 mg of single food may have clinically meaningful efficacy (Blumchen, 2019). The alternate target dose arm of 4500 mg will enable evaluation of 300 mg per food source, a level shown to be efficacious in several single-OIT clinical studies. Specifically, recent publications of OIT in subjects allergic to peanuts demonstrated clinically meaningful levels of desensitization, with 62% to 67% of children passing a DBPCFC at 600 mg and 50.3% passing at 1000 mg in the Intent-to-Treat (ITT) analysis (Bird, 2018; Vickery, 2018).

The dosing regimens to be used in this study are based on the dosing regimens and ranges of doses successfully used in previous mOIT studies (Begin, 2014b). The starting dose of ADP101 will be 5 mg total protein divided equally across 15 food sources, which is equivalent to approximately 0.3 mg for a single food source. For the purpose of the study, foods in ADP101 that are not allergenic for a particular subject are considered nutritive excipients. For subjects

with allergies to 5 food sources, the maximum total amount to which a subject has a qualifying allergy that would be given as a starting dose would be approximately 0.3 mg/food × 5 foods = approximately 1.6 mg. Hence, the starting doses range from approximately 0.3 mg to approximately 1.6 mg (depending on number of baseline allergies), levels that are generally lower than eliciting doses for a single allergen (Purington, 2018; Allergen Bureau, 2019; Remington, 2020), and lower than the recommended baseline starting doses for DBPCFCs (Sampson, 2001).

The basic schema of the dosing regimen in this study comprises an initial dose of 5 mg on Day 1, followed by daily dosing of 5 mg for 2 weeks. This dosing regimen is repeated, with updosing occurring every 2 weeks until the randomized target dose of either 1500 mg/day (100 mg/food source, low-dose regimen) or 4500 mg/day (300 mg/food source, high-dose regimen) is achieved. Subjects who are unable to reach a dose level of 50 mg/day within 3 updosing attempts will be discontinued from study drug (refer to Table 5 for further guidance).

Subjects who reach a minimum dose level of 50 mg/day will continue in the updosing phase of the study, returning to the clinic every 2 weeks for updosing under medical supervision. If a subject is unable to updose to the next dosing level within 3 attempts, the site should contact the Study Medical Monitor for further guidance regarding additional updosing. Subjects unable to achieve updosing to their randomized target dose will be continued on the highest level they achieve through Week 40, as long as it is at least 50 mg of study drug. Refer to Table 5 for management of subjects who are unable to updose to 50 mg levels. Updosing steps are based on percentage increase of the food source over time to gradually increase exposure. The planned rate of increase in dosing is also within the ranges of prior OIT studies for both the rate of increase of individual foods and the total amount of allergenic protein across multiple foods (Anagnostou, 2014; Begin, 2014b; Bird, 2018; Vickery, 2018).

4.3.1. Rationale for Double-Blind, Placebo-Controlled Food Challenge and the Associated Dose Levels

The rationale to conduct DBPCFCs to relevant foods during subject screening is to confirm required study entry criteria for the subject to have at least 1 and no more than 5 qualifying FAs, i.e., the food source when administered via DBPCFC causes dose-limiting symptoms at or below the 100 mg level. The rationale to repeat DBPCFCs at study exit is to evaluate any changes to the threshold for clinical reactivity in DBPCFC after the treatment period by comparing the active vs. placebo groups. This is to enable the primary and secondary efficacy objectives of the study.

The DBPCFCs to be carried out in this study will be conducted in accordance with the international consensus–recommended guidelines (Sampson, 2012); however, the lower dose of 1 mg tested (as opposed to 3 mg) is slightly modified from the PRACTALL recommendations as a precautionary measure since the dose needed to elicit objective symptoms in 10% of the allergic population (ED_{10}) of several foods can be lower than 3 mg (Purington, 2018; Allergen Bureau, 2019; Remington, 2020).

The Screening DBPCFCs will progress through the dose levels in an unaltered sequence without repeating any dose to provide standardization of the amounts of food allergen protein that subjects are exposed to when being tested in the clinical study setting. A study by Baumert et al. has estimated that increasing the baseline threshold before immunotherapy from 100 mg or less

peanut protein to greater than or equal to 300 mg peanut protein post-immunotherapy reduces the risk of a subject experiencing an allergic reaction by more than 95% for 4 common food product categories that may contain trace levels of peanut residue (Baumert, 2018). Further increase in the threshold to 1000 mg of peanut protein had an additional quantitative benefit in risk reduction for all subjects reacting to 300 mg or less at baseline. In order to conduct a preliminary assessment of efficacy, the Exit DBPCFCs will assess the same levels as done at study entry, as well as evaluating higher doses up to 4000 mg; DBPCFCs up to 4000 mg per food source were done by other groups in previous studies (Begin, 2014b; Chinthrajah, 2019). While PRACTALL guidelines include 3500 mg as the top dose for food challenge, they also suggest that "*top doses might need to be higher for certain foods (e.g., those of which the usual portion contains relatively high amounts of protein, such as fish), patients, or situations*" and indicate the potential that higher protein doses limit the chance of false negatives when gauged by recurrence of symptoms during subsequent introduction of the food (Sampson, 2012). The higher doses will help in further understanding the clinical efficacy of ADP101, and, in particular, in assessing the potential for clinical synergy across the 15 allergenic food sources to enable higher amounts of the food to be ingested. The higher-challenge dose levels are believed to represent amounts of food allergen protein in excess of what might typically be encountered in an accidental ingestion of food allergen–contaminated protein; hence, analyses at the higher levels are exploratory evaluations.

4.4. Study Duration

For each subject, the study is expected to last as follows:

Screening period:	Up to 12 weeks
Treatment period:	Up to 50 weeks (includes 40 weeks of treatment plus up to 6 weeks for Exit DBPCFCs [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 drug treatment through EOT); the treatment period will consist of an updosing portion and a maintenance portion, which will be variable per subject.
Follow-up period:	Up to 2 weeks from EOT

4.5. End of Study Definitions

A subject is considered to have completed the study if he/she has completed the EOT visit (if he/she continues to the OLE) or the follow-up visit (if he/she does not continue to the OLE).

The end of the study is defined as the date of the last visit of the last subject in the study.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

To be eligible for participation in this study, subjects must meet all the following:

Age

1. Aged 4 to 55 years (inclusive) at the time of signing the informed consent form (ICF)

Type of Subject and Disease Characteristics

2. Clinical history of allergy to at least 1 of the foods contained in ADP101 (i.e., almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat)
3. Experience dose-limiting symptoms at or below the 100-mg dose level to at least 1 food source and no more than 5 food sources during the Screening DBPCFC

Contraception

4. All subjects who are of childbearing potential and their partners must agree to use highly effective contraception during the study (refer to Appendix 3 in Section 10.3). All subjects and their partners must continue to use highly effective contraception for 30 days after the last dose of study drug.
5. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
6. Female subjects not of childbearing potential must be either premenstrual or postmenopausal (defined as cessation of regular menstrual periods for at least 12 months) and are not required to use contraception.

Informed Consent

7. Subject and/or legally authorized representative (i.e., parent/guardian) must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.
8. Minor subjects must be capable of giving written assent as appropriate per the applicable age (per local regulatory requirements).

5.2. Exclusion Criteria

Subjects must be excluded from participating in the study if they meet any of the following:

Medical Conditions

1. Confirmed presence of > 5 FAs with dose-limiting symptoms at or below the 100-mg challenge dose level during the Screening DBPCFC of food sources contained in ADP101
2. History of severe or life-threatening episode(s) of anaphylaxis or anaphylactic shock within 60 days of the first Screening DBPCFC

3. History of EoE; other eosinophilic gastrointestinal disease; chronic, recurrent, or severe gastrointestinal reflux disease (GERD); symptoms of dysphagia (e.g., difficulty swallowing, food "getting stuck"); or recurrent gastrointestinal symptoms of undiagnosed etiology
4. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen
5. Severe asthma per 2007 National Heart, Lung, and Blood Institute (NHLBI) Criteria Steps 5 or 6 (see Section 10.5)
6. Mild or moderate asthma (2007 NHLBI Criteria Steps 1 through 4; Section 10.5), if uncontrolled or difficult to control, as defined by any of the following:
    - FEV_1 < 80% of predicted, or ratio of FEV_1 to forced vital capacity (FVC) < 75% of predicted, with or without controller medications (only for age 6 years or greater and able to do spirometry)

      OR
    - Inhaled corticosteroid (ICS) dosing of > 500 µg daily fluticasone (or equivalent ICS based on NHLBI dosing chart)

      OR
    - One hospitalization in the previous year for asthma prior to screening

      OR
    - Emergency room visit for asthma within 6 months prior to screening
7. Known malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
8. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

   Note: No testing for HIV is required unless mandated by the local health authority.
9. Known active hepatitis B infection (defined as hepatitis B surface antigen [HBsAg]–reactive) or known active hepatitis C virus (HCV) infection (defined as HCV RNA [qualitative] detected).

   Note: No testing for hepatitis B and hepatitis C is required unless mandated by the local health authority.
10. Uncontrolled diabetes.

    Note: Subjects with controlled diabetes are allowed (insulin is allowed).
11. Hypertension requiring > 2 antihypertensive medications
12. Known history of cardiovascular disease, including, but not limited to, history of myocardial infarction or arterial thromboembolic events within 6 months prior to enrollment, severe or

unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a history of corrected QT (QTc) interval > 470 ms (Dickinson, 2005)

Note: Well-controlled hypertension is not considered to be part of this definition; see exclusion criterion 11 above.

13. History of interstitial lung disease
14. History of confirmed mast cell disorder, including mastocytosis, urticaria pigmentosa, or hereditary or idiopathic angioedema
15. History of celiac disease and/or any significant non-IgE–mediated intolerance (e.g., severe lactose intolerance) to 1 or more of the food sources contained in ADP101
16. Active infection within 30 days of screening requiring systemic therapy
17. Female subjects who are pregnant or breastfeeding, or expecting to conceive, or male subjects planning to father children within the projected duration of the study
18. Active autoimmune disease that has required systemic treatment within 3 months (i.e., use of disease-modifying agents, corticosteroids, or immunosuppressive drugs)
19. Known psychiatric or substance-abuse disorders that would interfere with cooperation with the requirements of the study
20. History or current evidence of any condition, therapy, or clinically significant laboratory abnormality that might preclude safe participation, confound the results of the study, or interfere with the subject's participation for the full duration of the study, or for which it is not in the best interest of the subject to participate, in the opinion of the treating investigator

Prior/Concurrent Therapy (Relative to Screening)

21. History of regular steroid medication use (via intravenous [IV], intramuscular [IM], or oral administration) in any of the following manners:
    - History of daily oral steroid dosing for > 1 month during the previous year

      OR
    - Burst oral steroid course in the previous 1 month

      OR
    - > 2 burst oral steroid courses in the previous year ≥ 1 week in duration
22. In the "build-up phase" of immunotherapy (i.e., has not reached maintenance dosing for at least 2 weeks) to another non-food allergen (e.g., environmental allergen, bee venom, etc.)
23. Inability to discontinue antihistamines at least 5 half-lives before SPT and DBPCFC
24. Use of any therapeutic antibody (e.g., dupilumab, omalizumab, mepolizumab, reslizumab) currently or within the previous 6 months or 5 half-lives, whichever is longer
25. Use of any food immunotherapy (e.g., oral, sublingual, epicutaneous) currently or within the previous 12 weeks

26. Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), or calcium-channel blockers

Prior/Concurrent Clinical Study Experience

27. Currently participating in or have participated in a study of an investigational agent within 4 weeks prior to Screening or 5 half-lives of the other investigational agent, whichever is longer

Other Exclusions

28. Develops dose-limiting symptoms to placebo during the Screening DBPCFC
29. Hypersensitivity to epinephrine or any of the excipients in study drug
30. Residing at the same address as another subject (e.g., siblings) participating in this or any other OIT/mOIT study

5.3. Screen Failures

Subjects who sign the ICF but who do not enroll in the study will be termed as screen failures.

A minimal set of screen failure information will be collected to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes, but is not limited to, demography, screen failure details, eligibility criteria, and any SAE. Additionally, screen failure data using biomarker samples may be used for future exploratory data analyses.

Subjects who are not enrolled may be eligible to rescreen upon approval by the Study Medical Monitor. Some procedures may not need to be repeated upon rescreening.

6. STUDY DRUG

6.1. Study Drug Administered

Arm name	Active	Control
Study drug name	ADP101	Placebo
Type	Immunotherapy	Not applicable
Dose formulation	Oral formulation mixture of 15 individual food sources from commercially available food flours containing allergenic proteins (almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat) with excipients Each dose is formulated to contain equal parts by protein weight of each of the 15 individual foods in ADP101.	Powder containing excipient, aroma and flavor maskers, and coloring agents to achieve similar appearance and total weight as the active, in the same cup packaging as the active.
Unit dose strength(s)	5, 50, 200, 500, and 1500 mg total protein per unit	0 mg total protein per unit
Dose level(s)	Refer to Table 3 for dose level and regimens for updosing. For dose modification, refer to Section 6.5.2. For guidance regarding scheduled updosing clinic visits that may need to be adjusted due to measures to protect public health during a public health emergency, refer to Appendix 6 (Section 10.6).	
Route of administration	Oral administration, to be consumed daily	
Administration instructions	Study drug is to be mixed with a palatable, age-appropriate food or liquid (that is cool enough to be consumed) to which the subject is not allergic, and is to be consumed on a daily basis. Subjects should be instructed to wash hands immediately after completing preparation of dose and handling study drug containers. Subjects should be counseled regarding avoidance and management of potential cofactors related to their dosing; more information regarding these cofactors can be found in the IB. Subjects should be advised to return all containers (empty and full) to their clinical site at scheduled visits. For additional administration instructions, refer to study site Pharmacy Manual.	
Sourcing	Provided by the Sponsor or designee	
Packaging and labeling	All study drug will be packaged in foil-sealed plastic containers at a central packaging facility. Study drug will be labeled as required per local country requirement. Study drug will be shipped to the investigational site or the investigational site pharmacy in compliance with country-specific requirements for investigational products. Refer to Appendix 6 (Section 10.6) for guidance during a public health emergency.	

The updosing regimen is shown in Table 3 and should be followed as described in Section 6.5.1.

Table 3: Study Drug Updosing Regimen

Total Protein ADP101 per Day (mg)	Low-Dose Regimen	High-Dose Regimen	Increase (%)	Minimum Approximate Total Amount of Qualifying Reactive Food Source (for Subjects Allergic to 1 Food in ADP101) (mg)	Maximum Approximate Total Amount of Qualifying Reactive Food Source (for Subjects Allergic to 5 foods in ADP101) (mg)
5	X	X	—	0.3	1.6
20	X	X	303	1.3	6.6
50	X	X	150	3.3	16.6
100	X	X	100	6.6	33.3
200	X	X	100	13.3	66.6
400	X	X	100	26.6	133.3
700	X	X	75	46.6	233.3
1000	X	X	43	66.6	333.3
1500	X	X	50	100	500
3000	NA	X	100	200	1000
4500	NA	X	50	300	1500

Abbreviations: NA = not applicable.

6.2. Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of study drug. Study drug will be stored in a secure location at the site and maintained at controlled room temperature between 20°C and 25°C (68–77°F). Excursions between 15°C and 30°C (59–86°F) are allowed if less than 72 hours in duration; the range of 15°C to 30°C (59–86°F) may be referenced on study drug labels. The subjects/legally authorized representatives will be instructed to keep dispensed study drug at room temperature.
2. Only subjects enrolled in the study may receive study drug and only authorized site staff may supply study drug (for study drug supply during public health emergencies, refer to Section 10.6). All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.
3. The investigator, institution, or head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Subjects will be required to complete a daily dosing diary for dosing compliance.
5. Further guidance and information for the final disposition of unused study drug are provided in the study site Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study drug target dose level and blinded treatment assignment (ADP101 or placebo) using interactive response technology (IRT). 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 IRT will be provided to each site.

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 the Sponsor 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, the Sponsor 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.

Study drug will be dispensed to subjects/legally authorized representatives by study site personnel. Study drug will be distributed according to the study randomization code.

6.4. Study Drug Compliance

Under Title 21 of the Code of Federal Regulations (21 CFR Section 312.62) and International Council for Harmonisation (ICH) Good Clinical Practice Guideline (ICH E6), the investigator is required to maintain adequate records of the disposition of study drug, including the date and quantity of study drug received, to whom study drug was dispensed (subject-by-subject accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Original records for receipt, storage, use, and disposition will be maintained by the study site. This log will contain the identification of each subject and the date and quantity of study drug dispensed. All records regarding the disposition of study drug will be available for inspection by the study monitor. Compliance will be performed by collecting returned, unused study drug. Additional details regarding dispensing study drug can be found in the Pharmacy Manual.

6.4.1. Handling Missed Doses

Missed doses of study drug during the study can pose a significant risk to the enrolled subjects. The approach for handling missed consecutive doses of study drug is outlined in Table 4. Any missed doses during the treatment period of the study will be managed by the investigator.

Table 4: Handling Missing Doses during the Study

Number of Missed Doses	Action
1 dose or 2 doses in a row	The next dose would be the current dose level and could be given at home.
3 doses in a row	The next dose would be the current dose level and would be given under supervision at the site.
≥ 4 doses in a row, but ≤ 7 doses in a row	The next dose would be a reduced dose under supervision at the site with consultation of Study Medical Monitor.
> 7 doses in a row	Refer to Section 7.1.2 for stopping rules.

6.5. Updosing and Dose Modifications of Study Drug

6.5.1. Updosing and Downdosing of Study Drug

Initial updosing to a new level will be attempted sequentially every 2 weeks per the updosing regimens in Table 3. A telephone call follow-up will be done 1 day after each updosing visit to inquire about allergic symptoms and promote adherence to treatment, and remind subjects to complete the daily diary. As shown in Table 5, subjects who fail to tolerate dose levels of at least 50 mg/day will discontinue study drug; these subjects will remain in the study per Section 7.2.

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 who do not tolerate the current dose level may be permitted to downdose to a previous dose level at the discretion of the investigator.

Subjects must not be updosed for 3 days after the cessation of administration of corticosteroids.

For guidance regarding updosing during a public health emergency, refer to Appendix 6 (Section 10.6).

Table 5: Updosing Decisions for Study Drug

Dose Level Attempted during Updosing Phase (mg)	Tolerated Dose within 3 Attempts?	Instructions
5	Yes	Continue to the next dose level.
	No	Discontinue study drug and remain in the study per Section 7.2. An additional subject will be randomized without impacting the overall 2:2:1:1 randomization ratio.
20	Yes	Continue to the next dose level.
	No	Discontinue study drug and remain in the study per Section 7.2.
50	Yes	Continue to the next dose level; subject is eligible to continue the study.
	No	Discontinue study drug and remain in the study per Section 7.2.
Any dose above 50 mg	Yes	Continue to the next dose level.
	No	Contact Study Medical Monitor for further instructions.

In-Clinic Observation after Initial Study Drug Administration and Every Updosing

During initial study drug administration and at every subsequent updosing visit at the clinic, subjects with no or mild symptoms will be observed for 2 hours after dosing. For moderate to severe symptoms, the observation period after updosing should be at least 4 hours and up to 24 hours based on symptoms and the treatment regimen needed to stabilize the subject. For allergy symptom severity, refer to Table 11 (Consortium of Food Allergy Research [CoFAR] Severity Grading). For guidance on acute allergy symptom management, refer to the DISP in the Study Reference Manual; the DISP is to be provided to study subjects.

For specific questions related to updosing or continuation of the same dose that are not addressed in the protocol, the investigator should discuss the circumstances with the Study Medical Monitor for decision-making on next steps with regard to study drug.

6.5.2. Dose Modifications of Study Drug in the Setting of Allergic Adverse Events

At clinic updosing visits, subjects with active wheezing, PEFR < 80% of predicted, or a current flare of atopic dermatitis or other conditions that contraindicate updosing per the investigator's discretion will be maintained on their current dose of study drug until their flare of asthma or atopic dermatitis (or other condition) is resolved.

If a subject is suitable to undergo updosing and tolerates the in-clinic dose without symptoms, the action should be to continue per protocol with daily home dosing of the tolerated dose, with the next updosing visit 2 weeks later.

If the subject only experiences oral/pharyngeal pruritus during the administration of the daily dose, then the same dose can be repeated the next day at home and continued throughout the updosing 2-week period unless other symptoms begin to develop.

Table 6 provides an overview of actions with regard to study drug in the setting of allergic reactions by severity, which is also described below. Actions taken related to study drug dose modification should be driven by clinical picture and investigator judgment. For medication management of allergic reactions during the study, refer to Section 6.7. Refer also to the Study Reference Manual for additional details.

Table 6: Study Drug Dose Modifications by Allergic Adverse Event Grading

AE Grade per CoFAR	Options per Investigator's Clinical Assessment of AE and Relationship to Tolerability of Study Drug
Grade 1 (mild symptoms)	• Continue study drug at home and monitor for symptom worsening. • Dose subject at clinic under medical supervision. • Extend current dose level for up to another 2 weeks. • Reduce by one dose level for up to 2 additional weeks before attempting updosing.
Grade 2 (moderate symptoms)	• Subject to return to clinic for observed dosing at current level. – Reduce by 1 to 2 dose levels, with initial dosing in clinic, until dose tolerated with mild to no symptoms for up to 4 weeks. If mild symptoms are then observed, proceed as per Grade 1 (mild symptoms) above.
Grade 3 (severe symptoms)	• Hold dosing until subject returns to clinic (within 3 days). • Reduce by 1 to 2 dose levels until dose tolerated with mild to no symptoms for up to 4 weeks. – If mild symptoms achieved, proceed as per Grade 1 (mild symptoms) above. – If moderate to severe symptoms persist, consider another dose reduction by 1 to 2 doses. – If still not tolerated despite above, discontinue study drug.
Grade 4 (life-threatening symptoms)	• Discontinue study drug permanently.

Abbreviations: AE = adverse event; CoFAR = Consortium of Food Allergy Research.

6.6. Treatment of Overdose

For this study, any dose of study drug greater than the assigned daily dose will be considered an overdose. There is no specific treatment recommended to treat an overdose of study drug, and the subject should receive treatment directed toward any symptoms manifested.

In the event of an overdose, the investigator should do the following:

1. Contact the Study Medical Monitor as soon as possible.
2. Closely monitor the subject for any AE/SAE. In case of any observed event(s), note that the event(s) occurred after an overdose.
3. Document the quantity of the excess dose, as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Study Medical Monitor based on the clinical evaluation of the subject.

6.7. Medication Management of Allergic Adverse Events

Systemic allergic reactions (including anaphylaxis) that occur on study drug should be treated as appropriate to the subject's clinical picture and may include epinephrine, IV fluids, albuterol,

antihistamines and/or steroids. Generally, for mild and moderate symptoms, the subject may receive antihistamines in addition to other medicines as may be appropriate per the investigator's discretion. For more severe symptoms, the subject should receive epinephrine, antihistamines, and then the other medications, as indicated. All systemic allergic AEs should be evaluated for anaphylaxis as defined in Section 10.4.1. If there is any doubt regarding the severity of the reaction, epinephrine should be used for treatment.

All subjects will be provided with and trained on the DISP (refer to the Study Reference Manual) in order to manage any acute reactions they have when home-dosing. In addition, after recording their dosing daily in the electronic diary, subjects will be prompted to record whether they had any symptoms related to dosing.

Subjects and/or legally authorized representatives enrolled in this study will be confirmed to have 2 nonexpired EAI devices at the time of study entry and during each subsequent study visit. Subjects and/or legally authorized representatives will be trained in proper use and should be able to demonstrate proper technique with the EAI device as part of the DISP at time points specified in the SoA (Section 1.3).

For guidance regarding accidental exposure, refer to the FAAP form (Food Allergy Research and Education, 2018). During a public health emergency, refer to the "*Revised Anaphylaxis Management Algorithm During the COVID Pandemic*" (Food Allergy Research and Education, 2020).

Localized allergic symptoms may occur during the treatment period as an expected response to study drug. Recommendations for the management of specific symptoms are summarized in Table 7. For rescue medications, refer to Section 6.8.1. For guidance on allergy symptom severity, refer to the CoFAR severity grading system (Table 11).

Table 7: Overview of Localized Allergic Symptoms and Corresponding Recommended Medication Management

Symptom	Recommended Medication Management
Localized gastrointestinal symptoms	Manage first with H2-blockers (e.g., Pepcid® or equivalent) and antacids, with the potential to advance to treatment with proton-pump inhibitor, ondansetron (Zofran®), and potentially fluticasone propionate (Flovent®), as per the clinical picture. Subject's symptoms should be evaluated for the presence of eosinophilic esophagitis if indicated by the symptom profile (refer to Section 10.4.2).
Throat itching	Use ice chips/throat lozenges for throat irritation prior to considering other therapies for symptoms that do not resolve.
Upper airway symptoms (nasal congestion, rhinorrhea, sneezing, pruritis)	Use over-the-counter medications (e.g., second-generation antihistamines) to manage upper airway symptoms (e.g., decongestant for rhinorrhea and nasal congestion).
Lower airway symptoms (wheezing, cough, dyspnea)	Use inhalers, nebulizers for wheezing.
Skin symptoms (erythema, pruritus, hives)	Use over-the-counter medications to manage symptoms (e.g., topical applications with corticosteroids).

Symptom	Recommended Medication Management
Ocular symptoms (pruritus, conjunctival erythema, tearing, periorbital edema)	Use over-the-counter medication to manage symptoms (e.g., artificial tears, decongestant eye drops with or without antihistamine, mast cell stabilizers) (Richards, 2015).

Notes: For systemic allergic reaction (i.e., multisystem) see Section 6.5.2.

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines) or vaccine that the subject is receiving at the time of screening or receives during the study will be recorded.

There are no protocol-mandated concomitant medications, with the exception of requiring the availability of 2 nonexpired EAI devices to use as needed for an allergic reaction. Concomitant medications necessary for the health and well-being of the subject, including management of commonly comorbid conditions, that do not interfere with study assessments and are not excluded per Section 6.8.2 are permitted during the study at the investigator's discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the investigator. All medications must be recorded in the source documentation and on the appropriate electronic case report forms (eCRFs).

All subjects may continue their usual medications other than prohibited medications (Section 6.8.2), including those taken for asthma, allergic rhinitis, and atopic dermatitis, during the study. However, they must be able to discontinue antihistamines prior to SPT and DBPCFC. Antihistamine treatment will be allowed as described in Table 8 (second-generation antihistamine treatment is recommended). Regular topical steroid use is permitted at the time of skin testing, and testing will proceed if there is a sufficient area of skin surface not being treated with topical corticosteroids available for SPT placement. If there is an insufficient area of skin surface not being treated with topical corticosteroids, the SPT should be rescheduled to a time when enough skin surface is available that is not being treated with topical corticosteroids or discontinuation of topical corticosteroids (whichever event is sooner).

The Study Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Table 8: Antihistamine Treatment Stipulation

Timing with Respect to Study Drug Treatment	Allowed/Not Allowed
< 5 half-lives before skin-prick test	Not allowed
< 5 half-lives before DBPCFC	Not allowed
After treatment with study drug	Allowed
For treatment of coexistent atopic conditions	Allowed

Abbreviations: DBPCFC = double-blind, placebo-controlled food challenge.
Notes: Refer to DBPCFC Manual for half-life information based on antihistamine class.

6.8.1. Rescue Medications

For allergic reactions to food allergens that may occur during the DBPCFC, subjects will be treated with epinephrine at the discretion of the investigator. Epinephrine is used early during allergic reactions to food allergens to prevent these reactions from becoming more severe. Subjects should already have 2 EAI devices (EpiPen® or equivalent device) with them during the clinical visits (and at all times), but for those who do not, an EAI prescription will be provided at study entry. Study staff must ensure that the subjects/legally authorized representatives have been trained in its proper usage, including injection technique. A periodic refresher of more detailed training for subjects on the FAAP and DISP will occur during the study.

Treatment of allergic reactions during the DBPCFC, study drug dosing, and SPT may also require antihistamines, IV fluids, beta-adrenergic agonist (e.g., albuterol), oxygen, corticosteroids, and/or epinephrine, as indicated. These medicines need to be readily accessible at the study site prior to beginning any DBPCFC, clinic dosing/updosing, or skin-prick testing. See also Table 7 in Section 6.7. Subjects must have access to 2 nonexpired EAIs throughout the study as recommended by the "*Revised Anaphylaxis Management Algorithm During the COVID Pandemic*" (Food Allergy Research and Education, 2020) and general good practices.

6.8.2. Prohibited Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the study (see Section 5.2). If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study drug may be required. The investigator should discuss any questions in that regard with the Study Medical Monitor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study drug requires the mutual agreement of the investigator, the Sponsor, and the subject and/or legally authorized representative.

The following medications are prohibited during the study:

- Any systemic immunomodulatory (including immunosuppressive) agent, such as, and not limited to, dupilumab, omalizumab, reslizumab, and mepolizumab
- Food immunotherapy (e.g., oral, sublingual, epicutaneous), with the exception of study drug
- Systemic corticosteroids (administered orally, intravenously, or intramuscularly) used for any longer duration than a total of 3 consecutive weeks throughout the study. If corticosteroids are used during the study, subjects must not be updosed for 3 days after the cessation of administration of corticosteroids.
- Beta-blockers (oral)
- ACE inhibitors
- ARBs
- Calcium-channel blockers
- Investigational agents

6.9. Intervention after the End of the Study

Subjects taking either ADP101 or placebo who complete the study (EOT visit), and agree to participate via a separate consent process may be eligible to receive treatment with ADP101 through an OLE (described in a separate protocol [ADP101-MA-02]). Subjects who do not enroll in the OLE should be counseled by their physician/investigator as to the potential of resensitization.

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT WITHDRAWAL FROM THE STUDY

7.1. Stopping Rules

7.1.1. Study Stopping Rules

The study will be suspended if any of the following occurs:

- A treatment-related death occurs in a subject receiving ADP101, while the case is reviewed by the iDMC and the Study Medical Monitor (refer to Section 9.6 for the iDMC).
- A treatment-related CoFAR Grade 4 anaphylaxis event occurring in at least 3 enrolled subjects receiving ADP101 (refer to Table 11 and Section 10.4.1).
- A treatment-related biopsy-confirmed EoE event occurring in at least 3 enrolled subjects receiving ADP101.

  An EoE Adjudication Committee will be established for this study. If 3 cases of biopsy-confirmed EoE assessed as related to ADP101 occur during the course of this study, the iDMC will convene for an overall study review to recommend whether the study should continue (refer to Section 9.6). The study will be suspended while the 3 cases of EoE are reviewed; further steps with regard to the overall study conduct will be made by the Sponsor.

Suspension of the study will entail halting the enrollment of new subjects and maintaining enrolled subjects at their current dose levels and refraining from any updosing. Suspension of the study will not entail cessation of dosing unless so directed by the regulatory agencies, or advised by the iDMC and agreed to by the Sponsor. The suspension will remain in effect until the case(s) and supporting information have been discussed between the Sponsor and the iDMC and the relevant regulatory agencies, if applicable, with a decision made to either resume updosing or stop the study. If a decision is made to stop the study, all subjects will immediately discontinue dosing with study drug and will undergo a follow-up visit as specified in the SoA.

The iDMC will review safety data at regular intervals, and can recommend, in its judgment, halting the study for any substantial imbalance in AEs, apart from dosing symptoms expected during OIT with active drug. Sponsor additionally reserves the right to stop the study at any time for any reason. The regulatory health authorities and institutional review boards (IRBs)/independent ethics committees (IECs) will be notified in the event the study is stopped.

7.1.2. Individual Stopping Rules

Individual stopping rules related to study drug dosing are the following:

- Four or more consecutive missed days on at least 4 occasions due to noncompliance
- > 7 consecutive days of missed dosing due to noncompliance
- Life-threatening anaphylaxis resulting in severe hypotension, defined as systolic blood pressure (BP) below the fifth percentile for age (Banker, 2016), neurological compromise, oxygen saturation < 92%, or mechanical ventilation secondary to study drug dosing or any food challenge

- Nonresponse to 3 or more doses of epinephrine for treatment of a single dose-related allergic reaction

7.2. Discontinuation of Study Drug

It may be necessary for a subject to permanently discontinue study drug prior to planned completion of the treatment regimen per predefined stopping rules (see Section 7.1 above), or a subject may discontinue study drug for reasons including, but not limited to, the following:

- Adverse event
- Lost to follow-up
- Noncompliance with study drug
- Investigator decision
- Pregnancy
- Protocol deviation
- Termination of study by Sponsor
- Withdrawal by subject/legally authorized representative

The reason for subject discontinuation from study drug will be recorded in the source documentation and on the appropriate eCRF.

Permanent discontinuation of study drug does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete all study visits as per the SoA (Section 1.3); for these subjects, the Exit DBPCFC at Week 40 will be optional and at the discretion of the subject and investigator. The investigator is encouraged to consult with the Study Medical Monitor (or designee) prior to determining whether a subject should take part in the Exit DBPCFC in this situation.

7.2.1. Pregnancy

A subject who becomes pregnant must permanently discontinue study drug. See the SoA (Section 1.3) for data to be collected at the time of study drug discontinuation and follow-up, and for any further evaluations that need to be completed.

7.3. Subject Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the institution. Subjects may withdraw from the study for reasons including, but not limited to, the following:

- Death
- Withdrawal by subject/legally authorized representative
- Lost to follow-up
- Termination of study by Sponsor

The reason for subject withdrawal from the study will be recorded in the source documentation and on the appropriate eCRF.

If a subject is withdrawing from the study and has previously discontinued study drug, if possible, an Early Termination (ET) visit should be conducted, as shown in the SoA (Section 1.3). If the subject is simultaneously discontinuing study drug and withdrawing early from the study, the ET visit should be conducted. The subject should be encouraged to return for the follow-up visit. See the SoA for data to be collected at the time of study withdrawal and at follow-up and for any further evaluations that need to be completed.

7.4. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- The Sponsor may also attempt to ascertain vital status on subjects deemed lost to follow-up.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Significant safety concerns should be discussed with the Sponsor immediately upon occurrence and site awareness to determine whether the subject should continue or discontinue study drug.
- Adherence to the protocol and assessments, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- This study will use a mobile application (mApp) for participating subjects, the functionality of which is the following:
  - Prompt subjects to take their daily dose of study drug (subject daily dosing diary)
  - Record dosing
  - Inquire about any dose-related symptoms
  - Alert sites to potential AEs
  - Capture any potential reactions due to an accidental exposure to subjects' allergic food(s)
- For public health emergency situations, sites should refer to Appendix 6 (Section 10.6) for guidance.

8.1. Efficacy Assessments

Planned time points for efficacy assessments are provided in the SoA.

8.1.1. Double-Blind, Placebo-Controlled Food Challenge Procedure

The DBPCFC procedure used in this study, considered to be the gold standard for diagnosing FA, is based on the PRACTALL Consensus Guideline published in 2012 (Sampson, 2012); however, the updose schedules are slightly modified from the PRACTALL recommendations, and are presented in Table 9. The maximum dose will be 1000 mg for the Screening DBPCFC (Figure 2) and 4000 mg for the Exit DBPCFC (Figure 4). To ensure subjects are at their baseline state of health prior to each DBPCFC, subjects will have an adequate interval between individual food challenges (for suspected multi-allergy subjects requiring a series of DBPCFCs), as assessed by the Investigator, to account for rescue medication washout, requisite pre-challenge assessments and to demonstrate adequate control of atopic disease and subject safety prior to each subsequent DBPCFC.

Refer to the DBPCFC Manual for more information.

Prior to initiating a DBPCFC, the following will occur:

- Subjects will be asked to restrict the use of drugs that could interfere with the assessment of the DBPCFC, including, but not limited to, oral antihistamines (5 half-lives), beta-agonists (12 hours), theophylline (24 hours), and cromolyn (12 hours) (refer to Table 8).
- Subjects will have their oxygenation status recorded via pulse oximetry. Subject oxygen status must be > 95% to continue with the food challenge procedure (refer to Section 8.2.6).
- All subjects (aged 6 years or older) will undergo spirometry regardless of medical history and must have an FEV_1 > 80% of age predicted prior to starting the DBPCFC procedures. Subjects aged 4 to < 6 years will undergo a pulmonary function assessment as described in the DBPCFC Manual.
- Subjects with a history of asthma will be assessed for worsening of asthma symptoms as determined by active wheezing or a PEFR < 80% of predicted prior to each food challenge. If worsening asthma symptoms are present, the food challenge will be rescheduled until the subject is without wheezing and demonstrates pulmonary function > 80% of age predicted level.
- Subjects must be free from a flare of atopic disease (e.g., atopic dermatitis) or suspected intercurrent illness at the time of the DBPCFC.
- Subjects must be fully recovered, i.e., back to their baseline state of health, from any preceding illness for at least 3 days, depending on investigator-determined suitability, to be able to continue in the study.

Before each challenge, the subject will have a physical assessment administered by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material.

Oral food challenges will be undertaken under direct medical supervision and with emergency medications and trained staff immediately available. A physician or qualified clinician designee will oversee the DBPCFC. This physician or qualified clinician designee will be blinded to the content of each food challenge, and will assess the subject's reactions at Screening and Exit DBPCFC using a Food Challenge Symptom Score sheet (refer to the DBPCFC Manual). To the extent practicable, the same physician or qualified clinician designee who oversaw the Screening DBPCFC should oversee the Exit DBPCFC. The order of the foods tested will be random and blinded for each subject in order to eliminate the potential for bias by the assessing personnel.

The food challenge is performed by feeding gradually increasing amounts of a suspected allergenic food, with the food challenge material to be provided by the Sponsor, mixed with a palatable food, under physician or qualified clinician observation in accordance with the PRACTALL consensus guidelines. If the study team suspects a reaction may be developing, it may exercise its clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The placebo challenge will consist of placebo material given in the same number of doses and similar volume of dose material as in the active food sources (volumes of each of the active food challenges vary based upon the percentage protein content of the food).

If the subject begins to have any objective symptoms or subjective symptoms deemed significant per the PRACTALL guidelines (Sampson, 2012) (refer to the DBPCFC Manual), the food challenge will be terminated, and the subject will be given appropriate treatment. The subject will be observed by physician or qualified clinician designee for a minimum of 2 hours after the final administered dose and allowed to leave the site only when deemed clinically stable by a study physician.

Table 9: DBPCFC Doses at Screening and Exit

Type of Test	Screening	Exit
Doses (mg)	1	1
	3	3
	10	10
	30	30
	100	100
	300	300
	600	600
	1000	1000
		2000
		4000
Comments	The Screening DBPCFC will consist of 8 doses of food source given every 15–30 minutes in increasing amounts up to 1000 mg of food protein.	The Exit DBPCFC will consist of 10 doses of food source given every 15–30 minutes in increasing amounts up to 4000 mg of food protein.

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

8.1.1.1. Criteria for Double-Blind, Placebo-Controlled Food Challenge

Screening

Eligible subjects will be required to undergo a DBPCFC to specific food(s) at Screening if they meet ANY of the following criteria for an individual food source (see Figure 2 and Figure 3):

- A positive clinical history, including significant cross-reactivity to a known FA, for example, to cashews if allergic to pistachios (Section 4.2.2.1)
- If the clinical history of a particular food is unknown because a subject has never consumed that food or has had no recent exposure to the food, then a DBPCFC will take place if a mean wheal diameter of > 3 mm above negative control on an SPT at Screening is observed.

Based upon the outcomes of the DBPCFCs, foods that are challenged will be categorized into 2 groups: Reactive Foods and Non-reactive Foods.

Reactive Foods (at ≤ 1000 mg) will be confirmed on the basis of dose-limiting symptoms at or below the 1000-mg dose level of the specific food source during the Screening DBPCFC. To qualify for study participation, subjects must have dose-limiting symptoms at or below the 100-mg dose to least 1 and no more than 5 foods contained within ADP101 (these will be further

categorized as Qualifying Foods). Foods that were challenged to which the subject had a reaction above 100 mg will be further categorized as Non-qualifying Foods.

Foods that do not meet the above criteria at screening will be considered Non-reactive Foods; the subject will not undergo a Screening DBPCFC for these foods, as the subject will be considered not allergic to these foods based upon clinical history and biomarker evaluation.

When subjects undergo a Screening DBPCFC for a food and are able to tolerate the food challenge through the 1000-mg dose level, this food will also be considered a Non-reactive Food for the subject at Screening.

Exit/Week 40

Subjects who complete updosing to at least the 50-mg dose level by Week 40, regardless of treatment assignment, will undergo Exit DBPCFC(s) as outlined below.

All Reactive Foods (both Qualifying and Non-qualifying) will be challenged at the Exit DBPCFCs. The rationale for challenging Non-qualifying Foods at Week 40 is to determine whether the subject's FA improved or worsened on treatment.

Subjects will not have an Exit DBPCFC for Non-reactive Foods unless there is a change in clinical symptoms and/or SPT results (see Figure 4). Hence, an Exit DBPCFC will be triggered for the individual Non-reactive Foods at Screening when one of the following is present:

- Allergic symptoms during recent food consumption

  OR

- For foods that were not recently consumed, an increase in SPT mean wheal diameter ≥ 3 mm (relative to negative control) at Week 38 relative to screening

Only symptomatic evidence on the Exit DBPCFC would meet the criteria for a new food sensitization at study exit to a previously Non-reactive Food at Screening.

8.1.2. Patient-Reported Outcome

PRO instruments are essential to the measurement of health status and FA impact on subjects. The impact of FAs manifests in fear, anxiety, and other effects (Shaker, 2017; Renz, 2018) that can only be measured by directly asking the subject. Quality of life (QoL) related to FA has been studied in both adults and children (Morou, 2014; Antolin-Amerigo, 2016). In order to understand how ADP101 affects a subject's FA-related QoL over time, the PROs listed below will be administrated at time points specified in the SoA (Section 1.3).

8.1.2.1. Food Allergy Quality of Life Questionnaire

The FAQLQ is a disease-specific HRQoL questionnaire for subjects with FAs. This questionnaire has versions for children aged 8 to 12 years (FAQLQ-Child Form [CF]), adolescents aged 13 to 17 years (FAQLQ-Teen Form [TF]), and adults (FAQLQ-Adult Form [AF]), as well as a proxy version for parents of food-allergic children up to 12 years of age (FAQLQ-Parent Form [PF]). Each version contains 3 or 4 domains to assess different aspects of FA-related HRQoL (Table 10). The FAQLQ versions have all demonstrated good reliability and validity and have shown responsiveness when changes occur (Flokstra-de Blok, 2009;

van der Velde, 2009; DunnGalvin, 2010; Wassenberg, 2012). Each item employs a 7-point response scale rating from minimal impairment to maximal impairment. Total FAQLQ scores and domain scores are calculated by dividing the sum score of completed items by the number of completed items.

Refer to the Study Reference Manual for more details.

Table 10: Food Allergy Quality of Life Questionnaire Domains

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.

8.1.2.2. Accidental Exposure Questionnaire

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 ADP101 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.

8.1.2.3. Immunotherapy-Related Quality of Life

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 patients 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.

8.1.2.4. Treatment Satisfaction Questionnaire for Medication

The TSQM-9 is a well-validated, self-administered, 9-item questionnaire developed to assess the satisfaction that patients had with their medical treatment (Bharmal, 2009). The validity and reliability of the TSQM has been demonstrated in different patient groups (Atkinson, 2004). The TSQM-9 contains 3 domains, effectiveness, convenience, and global satisfaction, that together provide a measure of treatment satisfaction with medication from the patient's perspective. Each of the 3 domains contains 3 items. 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. It will be completed by the subject (or the parent for children < 12 years of age).

8.1.2.5. Food Allergy Quality of Life–Parental Burden Questionnaire

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 (Cohen, 2004). The FAQL-PB questionnaire was developed and validated on a US sample (Cohen, 2004), and has shown validity and reliability among parents of children with FA in multiple countries (Leung, 2009; Knibb, 2013). The questionnaire contains 2 domains, emotional distress and limitation on life, that include 14 and 3 items, respectively. Each item uses a 7-point response option rating from not troubled (or not limited) to extremely troubled (or limited). The total mean score for the questionnaire, mean score for each item, and mean score for each domain will be tabulated and critically assessed.

8.1.3. Medical/Surgical History, Food and Other Allergy Status

In addition to medical/surgical history assessment, subjects should be assessed for their experience with each of the 15 food sources included in ADP101. They should also be assessed for documented allergy status to allergens including, but not limited to, those in other food sources outside ADP101 (including fruits and vegetables), grass, pollen, insect venom, mites, cockroaches, dander, and epithelia. These data will help understand total allergic burden of subjects. Assessments should be performed within the time frame defined in the SoA.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin and cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- A brief symptom-directed physical examination will include, at a minimum, assessments of the skin and cardiovascular, respiratory, gastrointestinal, and neurological systems.
- The subject will be assessed for specific signs and symptoms of EoE.

8.2.2. Vital Signs

- Vital signs, including heart rate, temperature, and BP, will be measured after 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones).
- BP and heart rate measurements will be assessed with the subject in a sitting position or supine (lying face upward) with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs are to be taken prior to any blood draw that occurs at the same time point/visit.

8.2.3. Clinical Safety Laboratory Assessments

- See Appendix 2 in Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency. For additional details, refer to the Laboratory Manual.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or Study Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Study Medical Monitor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SoA.
  - If laboratory values from non–protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the appropriate eCRF.
- For guidance regarding laboratory assessments during a public health emergency, refer to Appendix 6 (Section 10.6).

8.2.4. Skin-Prick Test

Subjects will have SPTs performed using investigational site- and Sponsor-approved procedures for food allergens. Detailed instructions for performance of the SPT will be provided in the Study Reference Manual. Prior to the SPT, the investigator must ensure that the subject has not

received antihistamine medications for at least 5 half-lives of the medication. Commercial allergenic extract solution is introduced to the epidermis via lancet or skin prick for each of the 15 food sources to determine sensitivity to select foods that may be responsible for triggering symptoms in subjects with FA. In addition to allergens, positive (histamine) and negative (saline-glycerin) controls are also introduced to establish that the response is not blocked and to determine whether there is dermatographism, respectively. The positive and negative control tests should be performed and measured along with the allergen SPT.

8.2.5. Spirometry

Spirometry (FEV_1) and/or PEFR will be conducted in this study, if feasible. Spirometry assesses the integrated mechanical function of the lung, chest wall, and respiratory muscles by measuring the total volume of air exhaled from a full lung, including FEV_1.

In subjects 4 to < 6 years of age, a hand-held peak flow meter (PFM) will be used instead of spirometry. Spirometry is to be attempted in all subjects ≥ 6 years of age. For additional instructions, refer to the Study Reference Manual.

For guidance regarding spirometry in a public health emergency, refer to Appendix 6 (Section 10.6).

8.2.6. Pulse Oximetry

Prior to any food challenge or updosing procedure, subjects should have their oxygenation status recorded via pulse oximetry. Subject oxygen status must be > 95% to continue with the food challenge procedure.

8.2.7. Asthma

8.2.7.1. Asthma Severity Assessment

Asthma severity will be assessed by the investigator and documented during screening and at the Week 38 visit using the NHLBI Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 3 [EPR-3]) (National Asthma Education Prevention Program, 2007; Urbano, 2008). Refer also to Section 10.5.

Any asthma exacerbation events will be reported as AEs or SAEs as appropriate and will be summarized at study conclusion.

8.2.7.2. Asthma Control Assessment

Assessment of asthma control in asthmatic subjects using the Asthma Control Test (ACT) questionnaire (Schatz, 2006) or Childhood Asthma Control Test (C-ACT) questionnaire (Bime, 2016) will be performed as specified in the SoA.

For subjects aged 12 years and older, the ACT has 5 questions, each recorded on a scale of 1 (worst control) to 5 (complete control). The total ACT is the sum of the 5 scores, and ranges from 5 (worst control) to 25 (total control). A total score of 19 or less indicates that asthma is not adequately controlled. Missing data will not be imputed. If any of the 5 questions have a missing response, the total ACT score will not be calculated.

The C-ACT is validated for assessing asthma control in children aged 4 to 11 years (Liu, 2007). It includes 4 questions for the child and 3 questions for the parent to complete. Child responses range from 0 (worst control) to 3 (complete control). Parent responses range from 0 (every day) to 5 (no days). The sum of all 7 questions will make up the total score. The total C-ACT score for subjects under 12 years of age will range from 0 (worst control) to 27 (well controlled). A score of 19 or less indicates uncontrolled asthma. Missing data will not be imputed. If any of the questions have a missing response, the total C-ACT score will not be calculated for that subject.

A listing of the results from the questionnaire, including the total score, will be provided and sorted by treatment group, subject identification, and time point.

8.3. Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The definitions of AE, SAE, and adverse event of special interest (AESI) including anaphylaxis can be found in Section 8.3.1, Section 8.3.2, and Section 8.3.7, respectively. The AE severity grading is found in Section 8.3.3 for both allergic AEs (Section 8.3.3.1) and nonallergic AEs (Section 8.3.3.2).

AEs will be reported by the subject and/or legally authorized representative. Subjects will be instructed to complete a daily diary for dosing compliance and to prompt for any reactions after dosing. Symptoms reported by subjects in the diary will be reviewed by site personnel to evaluate for AE reporting.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.3.5.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.1. Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a subject temporally associated with the use of study drug during the clinical study, whether or not considered to be related to study drug. Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital sign measurements), including those that worsen from baseline, considered to be clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)

Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent preexisting condition other than the disease under study, including an increase in frequency and/or intensity of the condition • New conditions detected or diagnosed after study drug administration, even though they may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition • For medical or surgical procedures (e.g., endoscopy, appendectomy), the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

8.3.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study).

SAE Definition
An SAE is defined as any untoward medical occurrence that, at any dose:
• **Results in death**
• **Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. For anaphylaxis to be considered "life-threatening", it should have been assessed as a severity level Grade 4 allergic reaction (refer to Table 11).
• **Requires inpatient hospitalization or prolongation of existing hospitalization**

SAE Definition
In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for anaphylaxis should not have been solely for the sake of providing extended observation period, such as instances that may be utilized to monitor and manage a biphasic or delayed reaction, except in the case of intensive therapy as outlined in "other situations" below. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
• **Results in persistent disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Causes a congenital anomaly/birth defect**
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • For an anaphylactic event to be classified as an SAE on the basis of being an "important medical event", it should have resulted in an emergency room visit, and the emergency room visit should have been associated with intensive therapy. The investigator should determine what constitutes "intensive therapy", but this may include interventions such as IV epinephrine, intubation, or admission to an intensive care unit. – One or two intramuscular injections of epinephrine should ordinarily not be construed as "intensive therapy". • If an investigator elects to assess an episode of anaphylaxis to be an "important medical event" when the episode was of mild or moderate severity and did not require intensive therapy, the rationale for the investigator's assessment must be detailed in the event narrative.

8.3.3. Classification of an Adverse Event

8.3.3.1. Allergic Reaction Adverse Event Severity Grading

Allergic reactions will be graded according to the CoFAR grading system for allergic reactions, including events that meet the definition for anaphylaxis (Table 11). This approach is consistent with other industry studies in FAs (Vickery, 2018).

Table 11: CoFAR Severity Grading System for Allergic Reactions

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

Abbreviations: CoFAR = Consortium of Food Allergy Research.
Source: (Jones, 2017b).

8.3.3.2. Nonallergic Adverse Event Severity Grading

Assessment of Intensity

The severity of all nonallergic AEs will be evaluated by the investigator in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 (CTCAE v5.0). For AEs that are not adequately addressed in the NCI CTCAE, the investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal noninvasive intervention indicated (e.g., short course of antibiotics)
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
- Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
- Grade 5: Fatal outcome

It will be left to the investigator's clinical judgment to determine whether an AE is of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw consent from treatment due to what the subject perceives as an intolerable AE. If either of these situations arises, the subject should be strongly encouraged to undergo an ET assessment and be under medical supervision until symptoms cease or the condition becomes stable. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

8.3.3.3. Assessment of Causality

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- **Related**: An event is considered related if there is a reasonable possibility of causal association between the study intervention and the event. This means there is evidence to suggest a causal relationship between the study intervention and the AE. The AE follows a reasonable temporal sequence from the time of study intervention administration, follows a known response to the study intervention, and cannot be reasonably explained by other factors, such as the subject's clinical state or other therapeutic interventions, or concomitant drugs administered to the subject.
- **Not Related**: The available evidence supports that the event is related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the source documents that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator**

Assessment of Causality
always assess causality for every event before the initial transmission of the SAE data to the Sponsor. • The causality assessment is one of the criteria used when determining regulatory reporting requirements. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.3.4. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected at the time points specified in the SoA (Section 1.3).

Table 12 summarizes the different observation periods for AEs, SAEs, and AESIs.

Investigators are not obligated to actively seek AE(s) or SAE(s) after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from the study, and he/she considers the event to be reasonably related to study drug or study participation, the investigator must promptly notify the Sponsor.

Table 12: Adverse Event Collection Periods

Type of Event	AE	SAE	AESI
Reporting period	From consent until 14 days after last dose of study drug	From consent until 14 days after the last dose of study drug for all SAEs; SAEs considered related to ADP101 will be reported at any time until resolution/ stabilization of SAE.	From consent until 14 days after the last dose of study drug
Reporting timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Within 24 hours of the investigator's knowledge	Within 24 hours of the investigator's knowledge

Abbreviations: AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.

8.3.5. Recording and Follow-Up of Adverse Events and Serious Adverse Events

8.3.5.1. Recording of Adverse Events and Serious Adverse Events

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE, SAE, and AESI information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.

AE and SAE Recording
• There may be instances in which copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. However, for a reported case of anaphylaxis, the underlying events, including the respective severity, should be included (Table 11).

8.3.5.2. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits and contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4).

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health-care professionals. • If a subject dies during participation in the study or during an extension or follow-up period, the investigator will provide the Sponsor with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.3.6. Reporting of Serious Adverse Events

The following are regulatory reporting requirements for SAEs:

- Prompt notification of an SAE by the investigator to the Sponsor is essential (see Table 13) so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of study drug under clinical investigation are met.
- Sponsor will assess the SAE to determine whether it meets the suspected unexpected serious adverse reaction (SUSAR) reporting requirements. For SUSARs that meet the life-threatening and/or serious criteria for death, the Sponsor will report the SUSAR within 7 calendar days after initial receipt and for all other SUSARs, within 15 days.
- The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- An investigator who receives an investigator safety report from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Table 13: Serious Adverse Event Reporting to the Sponsor

SAE Reporting to the Sponsor via SAE Form
• The mechanism for reporting an SAE to the Sponsor will be by completing the study SAE form and emailing to the Sponsor's Pharmacovigilance team within 24 hours of becoming aware of the SAE. • Follow-up information will be recorded on the SAE form and must be transmitted to the Sponsor via email within 24 hours. Contact information for sending SAE form via email to: safetyreporting@syneoshealth.com

Abbreviations: SAE = serious adverse event.

8.3.7. Definition of Adverse Event of Special Interest

The following will be considered AESIs:

- Anaphylaxis, defined per Section 10.4.1.

  Any anaphylactic event will be recorded as an AESI. All events should be assessed to determine if they meet seriousness criteria graded as per Section 8.3.2.
- Any AE leading to the use of epinephrine (e.g., EAI)
- EoE (see Section 10.4.2 for details)

For information about management of AESIs, refer to the Safety Monitoring Plan in Appendix 4 (Section 10.4).

8.3.8. Reporting of Pregnancy

- Details of all pregnancies in female subjects and male partners of female subjects will be collected as outlined in Appendix 3 (Section 10.3).
- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3 (Section 10.3).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

8.3.9. Death Events

All death events will require completion of a specific death data collection page within the eCRF.

Timelines for reporting of death events are identical to the requirements for SAE reporting (see Table 12 and Section 8.3.6).

8.4. Biomarker Assessments

Biomarkers that may improve understanding of the biological mechanisms of FA and the impact of treatment with OIT, as well as potentially help identify subjects who may benefit from OIT, will be measured in this study. Hence, biomarker results from this study may benefit future efforts to identify noninvasive markers for FA diagnosis, predictors of DBPCFC outcomes, and response to OIT with ADP101.

The following blood biospecimens will be collected at prespecified time points as outlined in the SoA. Some markers will be analyzed throughout the course of the study, and others will be stored for batched biomarker analysis later in the study:

- Blood for measurements of relevant biomarkers, including, but not limited to, total and specific IgE, total and specific IgG4, cytokines, and microRNA
- Whole blood for isolation of peripheral blood mononuclear cells (PBMCs), which will be stored and analyzed for various immune-related biomarkers, including, but not limited to, T cell activation and repertoire
- Whole blood to analyze biomarkers related to, but not limited to, epigenetic changes in the DNA and T cell repertoire determination. Recent publications suggest that epigenetic changes in the DNA of a subject may be able to predict clinical reactivity (Alag, 2019b; a) and responsiveness to OIT.

Stool sample collection kits will be dispensed for this study. Stool samples will be used to determine the microbiome dysbiosis in subjects with FA and impact of OIT on the microbiome pre- and post-OIT with ADP101. Emerging data suggest that gut microbiome plays an important role in the development of FA (Feehley, 2019).

As biomarker science in the field of FA rapidly evolves, some of the biomarkers listed above (if deemed irrelevant at the conclusion of the study) may be replaced by potentially more relevant biomarkers. Blood samples collected and stored in this study may also be used to characterize the sensitization profile for different allergenic proteins, including, but not limited to, foods not included in ADP101, pollen, grass, insect venom, mites, cockroaches, dander, and epithelia. Stored samples may also be used for diagnostic development and allergen potency assays. The data from these assays may be submitted to regulatory authorities for relevant approvals.

All the data collected in this study will be explored using machine-learning approaches to develop potential predictors of clinical FA and DBPCFCs, and to identify subjects with FA who have the potential to derive benefit from OIT. Depending on the success of these initial approaches, there is the potential to study the findings in future independent studies of subjects with FA.

For guidance regarding biomarker assessment during a public health emergency, refer to Appendix 6 (Section 10.6).

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary endpoint is the proportion of subjects who tolerate at least 600 mg of a single qualifying food source without dose-limiting symptoms at the Exit DBPCFC.

The sample size for the study is sufficient to test for 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 arms).

9.2. 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 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 set of assumptions and calculations that follow is provided to show that the sample size of 16 subjects per active treatment arm vs. 8 subjects per placebo arm of the same dose arm is adequate to demonstrate that the ADP101 response rate is significantly higher than that of placebo in the pediatric population (≥ 4 to < 18 years old). Simulations for power calculations for the Fisher's exact test for each of 2 doses (vs. placebo) under alternative hypotheses were performed. Assuming placebo response rates of 4% and active response rates of 40% and 58% in the low- and high-dose regimen treatment arms, respectively (based on (Vickery, 2018)), and an alpha of 5%, power was calculated using 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.

Since each subject with a follow-up visit will provide a contribution to the analysis of response rates, all randomized subjects will be considered to be evaluable (as their follow-up duration will be at least 1 day), irrespective of whether they withdrew from the study prematurely.

Additionally, approximately 12 adult subjects will be randomized to the 2 doses of ADP101 (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.

Note: "Enrolled" means agreement of subjects, or their legally authorized representatives, to participate in a clinical study following completion of the informed consent process and randomization into the study after successful completion of the screening period. Potential

participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3. Populations for Analyses

The following populations are defined:

Analysis Population	Description
Screened	All subjects who are screened
ITT	All randomized subjects who receive at least 1 dose of the study treatment (analyzed as randomized). If no subjects receive the incorrect treatment, the ITT population will be the same as the Safety population. All demographic and baseline characteristic summaries will be based on this population. The primary and secondary efficacy parameters will be summarized based on this population.
Per Protocol (PP)	All subjects from the ITT population without any major protocol deviations that impact analysis (e.g., wrong inclusions, poor compliance, nonpermitted medications, noncompletion of 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 will be determined before database lock and treatment unblinding and will be specified in the statistical analysis plan.
Safety	All randomized subjects who receive at least 1 dose of study treatment (analyzed as treated). All safety parameters will be summarized based on this population. In case of deviation between randomized treatment and treatment actually received, the treatment actually received will be used in the safety analyses (i.e., an as-treated analysis will be performed).

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock (DBL) and will include a detailed description of the statistical analyses described in this section. The SAP will supersede this section of the protocol in the event of divergence. This section is a summary of the planned statistical analyses of primary and key secondary endpoints. Study conduct personnel will be unable to aggregate unblinded data until the database is locked and unblinded at the end of the study. iDMC members will have access to unblinded data for the purposes of reviewing safety data. Any deviations from the analysis planned in the SAP will be justified and recorded in the final clinical study report (CSR).

9.4.1. General Considerations

In general, descriptive statistics will be presented, including n (the number of observations), mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage (of non-missing values) per category for categorical data. Data will be summarized descriptively by treatment arm and overall.

9.4.2. Missing Data Handling

Missing efficacy data will be evaluated and modeled. The methods will be elaborated upon in the SAP.

9.4.3. Efficacy Analyses

For lists of objectives and endpoints, refer to Section 3.

Since the superiority of ADP101 at different doses over placebo will be tested, the primary and secondary efficacy analyses will be based on the ITT Population. The primary, secondary, and exploratory efficacy analyses will be performed on the ITT Population, as well as the PP Population (based on the ITT principle). Sensitivity analyses, to be described in full in the SAP, will be performed on subsets of the PP Population, e.g., including or excluding subjects who discontinue study drug prematurely due to treatment-related or unrelated reasons. For efficacy analyses, subjects will be analyzed according to randomized treatment.

Primary and secondary efficacy endpoints will be analyzed using Simes' Test with the Holms procedure (multiple p values will be elaborated in the SAP) and Fisher's exact test for dose selection. All individuals failing to achieve the success in the endpoint definition described above in Section 3 will be considered treatment failures. All individuals who drop out of the study or discontinue study drug prior to undergoing the Exit DBPCFC will be considered treatment failures (i.e., Missing = Failure).

Exploratory efficacy endpoints will be analyzed using descriptive statistics. Details will be included in SAP for the study.

9.4.4. Safety Analyses

All safety analyses will be performed on the Safety Population categorized by updosing and maintenance portions of the treatment period, as well as the blinded treatment extension and the follow-up periods. The safety assessment will be based on the frequency of AEs, observation of clinically significant abnormalities of laboratory values, concomitant medication use, and vital signs data in the Safety Population. Incidence rates of safety events adjusted by exposure in the maintenance dose level may also be reported.

9.4.4.1. Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be considered treatment-emergent if they start during or any time after the first dose of study drug until 30 days after the last dose of study drug. The incidence of treatment-emergent AEs will be summarized by treatment group, overall, System Organ Class and Preferred Term, and severity grade and relationship to study drug. SAEs and AEs leading to discontinuation will also be tabulated.

9.4.4.2. Vital Signs

The change from Baseline to each visit for each of the vital sign variables will be summarized by treatment group. Abnormal vital sign values will be flagged and listed.

9.4.4.3. Assessment of Asthma

Assessment of asthma severity in subjects with asthma via NHLBI criteria will be summarized by treatment group at baseline and at Week 38.

9.4.4.4. Clinical Laboratory

Clinical laboratory results (hematology and chemistry only) will be summarized by treatment group. All post-randomization laboratory values will be used to determine the incidence of potentially of clinical interest (PCI) laboratory values. The incidence of subjects with Sponsor defined PCI laboratory values will be presented.

Any subject with at least 1 PCI laboratory value will have all the values for that analyte listed.

Shift tables for all measurements will be provided, comparing baseline values with each subsequent visit whenever measured.

9.4.4.5. Concomitant Medications

Concomitant medications will be summarized for Preferred Term (generic name from the World Health Organization [WHO] dictionary) by treatment group. If 2 medications are coded to the same Preferred Term, they will be counted only once for a subject. Medications will be ordered alphabetically by drug class and Preferred Term within drug class.

9.4.5. Biomarker Analyses

Analysis of sIgE and other immunoglobulin biomarkers will be conducted and described in the SAP. Briefly, these biomarkers will be compared between Screening, Week 20, and Week 38. Descriptive statistics characterized by FA will be provided.

9.5. Interim Analysis

No interim analysis is planned.

9.6. 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 regular intervals during the study. 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, suspending enrollment (based on stopping rules; see Section 7.1) and halting the study for any substantial imbalance in AEs, apart from dosing symptoms. Guidelines for the operation and monitoring plans of the iDMC will be included in the 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 based upon the criteria described in Section 10.4.2, as well as to make a determination about suitability to continue on study treatment (refer to 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.

10. APPENDICES

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations, including Title 21 of the Code of Federal Regulations (21 CFR) Parts 11, 50, 54, 56, and 312
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated at that site.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent/Assent Process

- The investigator or his/her representative will explain the nature of the study to the subject and/or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where

applicable, and the IRB/IEC or study center. A legally authorized representative must consent to medical treatment for a person under the age of 18 years.

- The medical record must include a statement that written informed consent was obtained before the subject entered the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject and/or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.
- For more information regarding informed consent considerations during a public health emergency, refer to Appendix 6 (Section 10.6).
- The ICF will contain details about blood volume, storage, and use of biomarker samples.

10.1.3. Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- The subject and/or the subject's legally authorized representative must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject and/or the subject's legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

- A clinical study report will be written by the Sponsor according to the ICH E3 guidelines.
- The Sponsor will register the study and post-study results, regardless of the outcome, on a publicly accessible website (e.g., www.clinicaltrials.gov) in accordance with the applicable laws and regulations.

10.1.5. Data Quality Assurance

- All subject data relating to the study will be recorded on a printed or electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (e.g.,

laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Clinical Monitoring Plan. For more information regarding monitoring and risk mitigation considerations during a public health emergency, refer to Appendix 6 (Section 10.6).
- The Sponsor or designee is responsible for the data management of this study, including quality-checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator per ICH GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

- Source documents provide evidence of the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.7. Study and Site Closure

- The Sponsor, at its sole discretion, reserves the right to close the study site or terminate the study at any time and for any reason. All study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The investigator may initiate a study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of subjects by the investigator
  - Discontinuation of further study drug development

10.1.8. Publication Policy

- The publication policy is located within the Clinical Trial Agreement with the investigator and/or institution.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 14 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

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

Investigators must document their review of each laboratory safety report in subject's source documents.

Table 14: Protocol-Required 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 (hCG) pregnancy test (as needed for women of childbearing potential)	

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBPs:

1. Premenarchal
2. Premenopausal female subject with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

      For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

      Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female subject
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Female subjects on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception Guidance

Male Subjects:

Male subjects are eligible to participate if they agree to the following during the treatment period and for 30 days after the last dose of study drug:

- Refrain from donating sperm

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Be sexually active with women of non-childbearing potential

  OR

- Use contraception/barrier as detailed below:
  - Agree to use a male condom

Female Subjects:

A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and uses a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), at least 1 month prior to Screening, during the intervention period, and for 30 days after the last dose of study drug, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study drug.

  A WOCBP must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.

  If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly Effective Methods [a] that Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner (Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been

confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
Highly Effective Methods [a] that Are User-Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: – Oral – Intravaginal – Transdermal – Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation [b] – Oral – Injectable
• Sexual abstinence (Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

Notes: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

10.3.3. Collection of Pregnancy Information

Male Subjects with Partners who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the partner's pregnancy. The Sponsor or designee will attempt to follow the female partner to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or designee. The Sponsor will follow the female partner until birth or termination of pregnancy when possible. Any termination of the pregnancy will be reported to the Sponsor or designee regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor or designee. The subject will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported to the Sponsor or designee, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to study drug by the investigator will be reported to the Sponsor or designee as described in Section 8.3.5.2. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

10.4. Appendix 4: Safety Monitoring Plan for Adverse Events of Special Interest

10.4.1. Criteria for Suspected Diagnosis of Anaphylaxis

Consistent with other protocols investigating oral immunotherapy (OIT) (Andorf, 2018; Vickery, 2018), anaphylaxis is defined by the following criteria, adapted from the Second Symposium on the Definition and Management of Anaphylaxis: Summary Report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium (Sampson, 2006).

Anaphylaxis is likely when any 1 of the 3 following sets of criteria is fulfilled:

1. Acute onset of an illness (minutes to 2 hours) with involvement of the following:
    - Skin/mucosal tissue (e.g., generalized hives, itch or flush, swollen lips/tongue/uvula)

      AND

    - Airway compromise (e.g., dyspnea, stridor, wheeze/bronchospasm, hypoxia, reduced peak expiratory flow rate [PEFR])

      AND/OR

    - Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to likely allergen (minutes to 2 hours):
    - Skin/mucosal tissue (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula)
    - Airway compromise (e.g., dyspnea, stridor, wheeze/bronchospasm, hypoxia, reduced PEFR)
    - Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)
    - Persistent gastrointestinal symptoms (e.g., nausea, vomiting, crampy abdominal pain)
3. Reduced BP after exposure to the allergen (minute to 2 hours) as follows:
    - Infants and children: low systolic BP (age-specific) or > 30% drop in systolic BP

      Note: Low systolic BP for children is defined as < 70 mm Hg from age 1 month to 1 year; less than (70 mm Hg + [2 × age]) from age 1 to 10 years; and < 90 mm Hg from age 11 to 17 years.
    - Adults: systolic BP < 90 mm Hg or > 30% drop from their baseline

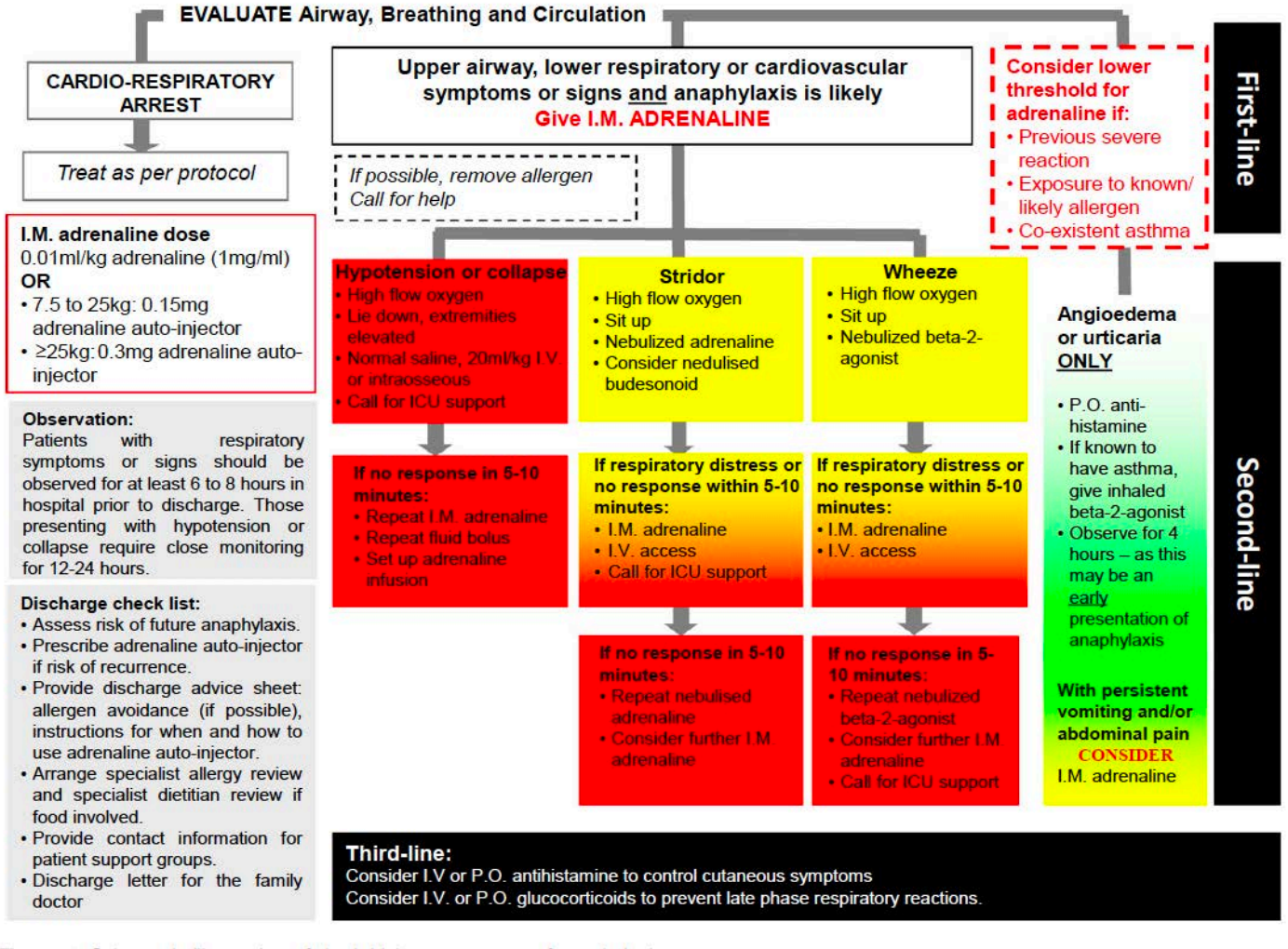
Note: Isolated skin or mucosal lesions following the ingestion of a food constitute a “food-induced allergic reaction.”

In case of anaphylaxis, study sites are responsible for handling anaphylaxis and having easy access to emergency services and transport/admission to local hospitals.

10.4.1.1. Management of Anaphylaxis during the Study

Management of suspected anaphylaxis in a health-care setting should occur per institutional standard of care. An example of the initial management of anaphylaxis as per the 2014 European Academy of Allergy and Clinical Immunology (EAACI) guidelines is included in Figure 5 (Muraro, 2014). The FAAP and the DISP will be provided to subjects, and will be located in the Study Reference Manual. Management of suspected anaphylaxis is provided in Figure 5.

Figure 5: European Academy of Allergy and Clinical Immunology Guidelines for the Management of Suspected Anaphylaxis



Abbreviations: ICU = intensive care unit; I.M. = intramuscular; I.V. = intravenous; P.O. = oral.
Notes: For stridor, consider nebulized budesonide.
Source: (Muraro, 2014).

10.4.2. Evaluation and Management of Eosinophilic Esophagitis

10.4.2.1. Background on Eosinophilic Esophagitis

Brief Description of Clinical Presentation

Based upon the latest international consensus statement (Dellon, 2018), EoE is a chronic immune- or antigen-mediated condition characterized by symptoms of esophageal dysfunction that requires both clinical and pathologic criteria to be formally diagnosed. Up to 75% of patients have a personal or family history of atopic disease (e.g., asthma, eczema, allergic rhinitis, and/or food allergy [FA]).

EoE appears to have had increasing prevalence in the overall population in recent years based upon epidemiologic studies (Ferreira, 2019). The prevalence of EoE in pediatric patients with immunoglobulin E (IgE)–mediated FA was higher than that reported in the general population (4.7% vs. 0.04%) in a large retrospective study (Hill, 2017). An additional prospective study of 128 patients undergoing OIT reported a prevalence of biopsy-confirmed EoE of 4.69% (Echeverria-Zudaire, 2016). In another study, the overall prevalence of EoE among patients undergoing OIT was estimated at 3% to 4% (Bird, 2018). In clinical studies with PALFORZIA, biopsy-confirmed EoE was reported in 12 subjects while receiving PALFORZIA (none in placebo) (PALFORZIA Package Insert, 2020).

In the setting of OIT to treat FA, clinical symptoms that may signal EoE may occur at any time during OIT dosing. Many symptoms of EoE also overlap with symptoms typical during OIT, and may therefore present a challenge when trying to attribute the source of the symptomatology.

Further complicating the evaluation, a recent single-center study (Wright, 2018) found that gastrointestinal eosinophilia (GE) is not uncommon at baseline in OIT subjects with IgE-mediated peanut allergy: preexisting esophageal eosinophilia (> 5 eosinophils per high-power field [eos/hpf]) was present in 5 of 21 adult subjects (24%), 3 (14%) of whom had > 15 eos/hpf associated with mild endoscopic findings without any clinical symptoms and hence were not diagnosed with EoE.

Mechanistic Understanding of Eosinophilic Esophagitis

Although the pathogenesis of EoE remains unclear, it likely results from an interplay of genetic, immune system, and environmental factors, as well as mechanisms of mucosal damage and fibrosis. Evidence suggests that the disease is associated with T helper cell 2 (Th2)–type immune responses, which are typical of other atopic conditions. EoE is believed to represent a mixed IgE- and non-IgE–mediated allergic response to food and environmental allergens. Given the chronic nature of the symptoms, it is currently postulated that non-IgE–mediated mechanisms predominate in EoE (Carr, 2018).

Consensus Criteria for Eosinophilic Esophagitis Diagnosis

Given the continued evolution in understanding of this disease, an international working group of thought leaders in gastroenterology, allergy, and pathology representing 14 countries was convened in 2017 (the AGREE [A working Group on ppi-REE] conference). The output of this

meeting established current EoE diagnostic criteria (Dellon, 2018). The 3 major criteria are as follows:

- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion of EoE
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion of EoE
- ≥ 15 eos/hpf (~60 eos/mm^2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

OIT has typically, but not always, been discontinued in the setting of suspected EoE based upon published practice from experts in the field (Sanchez-Garcia, 2012; Morais Silva, 2014). This approach often results in symptomatic improvement but leaves unclear whether the clinical symptoms were due to OIT, EoE, or both, particularly if formal evaluation for EoE, including esophagogastroduodenoscopies (EGDs) with biopsies, was not pursued.

There are studies that have evaluated continuing OIT in the setting of EoE. In a prospective study, OIT was maintained in 5 of 6 EoE subjects while proton-pump inhibitor (PPI) therapy with or without oral steroids was initiated. In all 6 subjects, symptoms resolved, and in 3 of the 5 subjects with repeat EGD, there was histological remission (Echeverria-Zudaire, 2016). Hence, there is variability in the management approach used in studies of OIT for the management of EoE cases that may occur.

Rationale for Dedicated Eosinophilic Esophagitis Evaluation in this Study and Role of the Eosinophilic Esophagitis Adjudication Committee

EoE has a higher prevalence among patients with FA, commonly comorbid atopic diseases, and during OIT. Diagnostic insights and criteria continue to evolve, and there are currently no international consensus guidelines specifically addressing EoE in the setting of OIT.

Although the general approach from the literature is to discontinue OIT in the setting of suspected or confirmed EoE, this is not universally the case in OIT studies, and it is possible that updated diagnostic and treatment recommendations may emerge over the course of this study.

Recognizing the potential for evolution in criteria for diagnosis and treatment of EoE, this study will empanel an EoE Adjudication Committee to review cases that may emerge during the study. Investigators and study site personnel will be asked to monitor all subjects carefully for symptoms of esophageal dysfunction at each study visit, and initiate an EoE evaluation if relevant symptom patterns occur (as described in Section 10.4.2.2) and management (as described in Section 10.4.2.3).

The EoE Adjudication Committee, composed of allergists and gastroenterologists with expertise in EoE, will be convened as described in Section 9.6. The purpose of the committee is to evaluate clinical information and confirm whether potential cases are suspected EoE, confirmed EoE, or unlikely EoE. This committee will also make recommendations on a case-by-case basis regarding next steps for study procedures, including study drug administration. This approach

will allow for real-time advice on evaluation and management of a subject according to the most current standard of care, recognizing that standard of care may evolve during the study.

10.4.2.2. Evaluation of Eosinophilic Esophagitis during the Study

Below is a brief summary of how EoE will be evaluated during this study; additional detailed information will be provided in the Study Reference Manual.

Screening

As noted in Section 5.2, all subjects with a history of clinically suspected and/or confirmed EoE will be excluded from study participation. For subjects for whom the history is uncertain, further discussion with the Study Medical Monitor is warranted to make a decision about eligibility for the study.

Post-Randomization Symptom Monitoring

All subjects will be evaluated at each study visit for the presence of symptoms that could be suggestive of esophageal dysfunction. These symptoms include, but are not limited to, difficulty swallowing, food impaction, food refusal, heartburn, regurgitation, vomiting, pain with swallowing, and abdominal pain. Since these symptoms overlap with OIT treatment more generally, the criteria outlined in Section 10.4.2.3 should prompt specific consideration for EoE evaluation, and should be pursued immediately.

10.4.2.3. Management of Eosinophilic Esophagitis during the Study

Eosinophilic Esophagitis Evaluation Criteria

An EoE evaluation should be initiated in the following settings:

- Moderate (Consortium of Food Allergy Research [CoFAR] Grade 2 or higher) symptoms of esophageal dysfunction daily for 7 days (Table 11)
- Moderate (CoFAR Grade 2 or higher) symptoms of abdominal pain daily for 14 days (shorter timeframes may be appropriate if the abdominal pain consistently occurs more than 2 hours after the daily dose of study drug is completed)
- Protracted vomiting for 5 days
- Any other constellation of recurrent symptoms that, in the investigator's judgment, indicates further evaluation to rule out potential EoE is warranted

Initiation of the Formal Eosinophilic Esophagitis Evaluation Process

EoE evaluation will be initiated by the investigator, and the Study Medical Monitor will be notified. A formal EoE evaluation process will be triggered either based upon the investigator's clinical evaluation alone or in consultation with the Sponsor/CRO study team in review of the constellation of symptoms being reported.

During the evaluation period for potential EoE, the investigator will be responsible for judging whether a subject is suitable to continue taking study drug and/or continue with study procedures.

Summary of the Eosinophilic Esophagitis Adjudication Committee Evaluation Process

Once the EoE evaluation process is initiated, the subject (with the help of a legally authorized representative , if needed) will be evaluated via the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) questionnaire, version 2.0, as part of an initial assessment (Martin, 2015); adults will be given the Eosinophilic Esophagitis Activity Index (EEsAI) (Schoepfer, 2014). Sites will also complete an SAE/AESI form with detailed narrative and detailed summary of the clinical picture and any relevant testing performed to date. Regarding additional site assessment of potential EoE, investigators will follow standard of care guidelines and institutional processes regarding referral to specialists (e.g., gastroenterologists) to help collect further clinically relevant evaluation information (additional blood work, imaging, repeat PEESS assessment, and referral for endoscopy evaluation with biopsies).

In parallel, the EoE Adjudication Committee will be convened to evaluate the details of the clinical case provided by the site, as well as the results of the PEESS or EEsAI assessment provided by the subject. The EoE Adjudication Committee may request additional clinical history, recommend further evaluations (e.g., additional blood work, imaging, repeat PEESS/EEsAI assessment, and referral for endoscopy evaluation with biopsies) to assist with its evaluation. The decision to do these additional evaluations remains with the investigator.

Once all of the information is gathered from the subject's EoE evaluation, the committee will provide the Sponsor (for further planning and communication with sites) with its assessment of the specific case as either suspected EoE, confirmed EoE, or unlikely EoE. A discussion will then occur between the investigator and the Study Medical Monitor regarding the results of the evaluation and next steps for the subject with regard to study procedures and/or study drug administration. Further details regarding EoE Adjudication Committee evaluation process are provided in the Study Reference Manual.

10.4.2.4. Study Participation following Completion of Eosinophilic Esophagitis Evaluation

If a subject discontinues study drug, the subject will be encouraged to continue remaining study assessments without treatment (and without Exit DBPCFC). If the subject chooses not to complete all study visits as per the SoA, the site will follow up with the subject every 2 weeks regarding status of his or her EoE-associated symptoms through the duration of the study or until suspected EoE-related symptoms have resolved (whichever is earlier).

10.4.2.5. Management of Eosinophilic Esophagitis

During the time period of EoE evaluation, it will be the investigator's decision about whether or not the subject should continue with study procedures and/or study drug based upon his or her symptomatology.

Given the nature of these symptoms, it is anticipated that subjects will have already had their dose level reduced or potentially held as part of general symptom management during OIT as outlined in Section 6.5.2.

Part of the EoE Adjudication Committee's remit includes the option of providing recommendations regarding symptomatic treatment for EoE (e.g., initiation of PPIs, oral steroids). If offered, these recommendations from the committee will be provided to the

investigator, who will make the decision about whether or not to implement the treatment recommendations in the subject.

Further details regarding EoE management are provided in the Study Reference Manual.

10.5. Appendix 5: National Heart, Lung, and Blood Institute Asthma Classification

The evaluation of asthma severity will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) classification published 28 August 2007, as described in Table 15.

Table 15: NHLBI Asthma Classification

Classification	Symptoms	Nighttime Awakenings	Lung Function	Interference with Normal Activity	Short-Acting Beta-Agonist Use
Intermittent (Step 1)	≤ 2 days per week	≤ 2× per month	• Normal FEV_1 between exacerbations • FEV_1 > 80% of predicted • FEV_1-to-FVC ratio normal [a]	None	≤ 2 days per week
Mild Persistent (Step 2)	> 2 days per week but not daily	3–4× per month	• FEV_1 ≥ 80% of predicted • FEV_1-to-FVC ratio normal [a]	Minor limitation	> 2 days per week but not > 1× per day
Moderate Persistent (Step 3 or 4)	Daily	> 1× per week but not nightly	• FEV_1 ≥ 60% but < 80% of predicted • FEV_1-to-FVC ratio reduced 5% [a]	Some limitation	Daily
Severe Persistent (Step 5 or 6)	Throughout the day	Often 7× per week	• FEV_1 < 60% of predicted • FEV_1-to-FVC ratio reduced > 5% [a]	Extremely limited	Several times per day

Abbreviations: FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; NHLBI = National Heart, Lung, and Blood Institute.

[a] Normal FEV_1-to-FVC ratio: 8–19 y = 85%, 20–39 y = 80%, and 40–59 y = 75%.

Adapted from (National Asthma Education Prevention Program, 2007).

10.6. Appendix 6: Guidance to Address Global Health Emergencies and Potential Impact on the Clinical Study

As of 12 March 2020, a coronavirus disease 2019 (COVID-19) pandemic has been declared by the WHO, leading to the implementation of extensive measures by health-care systems globally to limit viral spread, with potential impact on the conduct of clinical studies. This potential impact includes subjects/health-care workers in self-isolation/quarantine; limited access to public places, including hospitals; and health-care professionals with competing commitment to COVID-19 clinical care.

Based on guidelines issued by global regulatory authorities (Health Canada, 03 April 2020; MHRA, 22 April 2020; Australian Government, 2020; EMA, April 2020; FDA, March 2020), the actions listed below are being implemented in this protocol to address potential disruptions to study conduct secondary to Public Health Emergencies such as (but not limited to) COVID-19 infection or control measures. These actions are to assure the safety of study subjects, maintain compliance with GCP, and minimize the risks to study integrity.

General Site and Subject Safety Considerations

- COVID-19 screening procedures that may be mandated by the health-care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol, even if done during clinical study visits. The investigator, in consultation with the Sponsor, will decide whether it is in the best interest of COVID-19–positive subjects to remain in the study.
- Regarding COVID-19 status of staff and subjects, investigators should follow their local and institutional guidelines regarding testing, reporting, and management.
- In the event that investigators are made aware at any time of a subject's COVID-19 status change, investigators should follow the protocol, including eligibility criteria, individual stopping rules, and good clinical judgment, to assess the subject's ability to safely enroll or continue in the study.
- If a site has any subject with suspected or confirmed SARS-CoV-2, the site must notify the Study Medical Monitor.

Informed Consent

- If written consent by the study subject is not possible (for example, because of physical isolation due to COVID-19 infection), consent could be given orally by the study subject and/or the subject's legally authorized representative.
- If needed, the study subject and/or the subject's legally authorized representative and the person obtaining consent may sign and date separate informed consent forms.
- In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject and/or the subject's legally authorized representative by mail, facsimile, or e-mail, and the consent interview may then be conducted by telephone,

at which time the subject and/or subject's legally authorized representative can read the consent form during the discussion.

- If reconsent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to COVID-19 or important safety issues arising in this study), alternative ways of obtaining reconsent may include contacting the study subject and/or the subject's legally authorized representative via telephone or video-call to obtain oral consent, which would be documented in the study subject's medical records and supplemented with e-mail confirmation.
- The informed consent procedure is to remain compliant with the study protocol, as well as local regulatory requirements. All relevant records should be archived in the investigator's site master file. A signed and dated informed consent form should be obtained from the study subject and/or the subject's legally authorized representative as soon as possible.

Study Visits and Procedures

- In recognition of the potential for public health emergency status to change over time, subjects and/or legally authorized representatives enrolled in this study will be confirmed to have 2 nonexpired EAI at all times based upon the "*Revised Anaphylaxis Management Algorithm During COVID Pandemic*" (Food Allergy Research and Education, 2020).
- Local guidance may require a mandatory quarantine period for anyone traveling across state lines. Investigators should ensure that their study subjects are aware of these travel mandates and the potential impact on study visits and assessments.
- In the case of missed visits due to COVID-19 (or other health pandemic)–related reasons, the site should make every effort to contact the study subject to confirm and document the reason for the missed visit and, at a minimum, evaluate AEs/SAEs and concomitant medications in order to assess subject safety.
- To maintain the integrity of the study, if study subjects cannot access a clinical study site, alternative methods of collecting study procedures may be considered where possible and in certain situations, with Sponsor approval, as follows:
  - In cases in which a subject is continuing to receive study drug but COVID-19 pandemic-related circumstances preclude a visit to the clinical study site, remote visits (e.g., virtual visits by tele-visit or telephone contact) will be allowed for relevant study procedures while maintaining subject's privacy, as would be done for a clinic visit.
  - Study assessments will only be conducted in a remote manner if they can be done without affecting the well-being of the subject during the study and with the same level of scientific integrity as assessments conducted in a physical study center. Certain study visits, such as Screening and Exit DBPCFCs or initial updosing (every 2 weeks), will be required to be done in clinic to ensure the subject's safety. If the subject cannot come into the clinic to initial updose to a subsequent dose level, he or she will continue taking his or her current dose level, as long as

it is well-tolerated. The subject will continue on this dose level until he or she is able to return to clinic in person to be assessed for initial updosing to the next level.

- According to site business continuity plans, home visits or safe alternatives (e.g., drive-in clinics) may be used to collect laboratory samples and conduct other assessments as required by the protocol. Alternatively, the Sponsor may offer centralized solutions to ensure collection of laboratory samples and other assessments as required by protocol. In case a central laboratory cannot be used, sites may consider using a local laboratory.
- Data from subjects participating in remote visits/assessments may be collected electronically using purpose-built technology, or via traditional paper-based methods. AEs/SAEs (reporting, assessing, and follow-ups) will be handled similarly to a traditional model, with the subject contacting study personnel or engaging local care for emergencies.
- Missed assessments for primary and secondary endpoints should be discussed with the Sponsor for approval. In certain situations, with prior approval, other options or delayed visits can be considered.
- For assessments deemed to put subject and/or site safety at potential risk (e.g., spirometry) during a public health emergency, investigators are encouraged to identify and use, with prior Sponsor approval, alternative options (e.g., peak flow meter for spirometry in asthma assessment) to assess baseline patient health status for inclusion or continued participation in the study.

Study Drug Supply

- Alternative methods of supplying or disposing of study drug to enrolled study subjects (e.g., direct-to-subject shipment from site) may be considered where possible. Alternatively, the Sponsor may offer centralized solutions to ensure continuity of study drug supply as required by the protocol.
- Additional study drug will not be released to the subject without an evaluation of subject safety and approval by the investigator.
- Subjects will remain at the dose level reached and will not updose or undergo DBPCFC procedures if unable to attend in-clinic visits.
- Once public health emergency institutional guidance allows for clinic visits, the investigator is encouraged to resume study activities and attempt updosing to the subject's randomized target dose or the subject's highest tolerated dose.

Monitoring and Audits

- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site

monitoring), during a public health emergency are provided in the Clinical Monitoring Plan.

COVID-19 Vaccination

- Several vaccines for COVID-19 have been approved worldwide.
- The Sponsor does not have specific data regarding any possible interaction between the COVID-19 vaccines and ADP101 and has no evidence or rationale to suggest that ADP101 alters the vaccine's efficacy or increases the vaccine's toxicity.
- In the current study, COVID-19 vaccines are allowed as concomitant medication per the discretion of the Investigator, based on current standard of care and published guidelines, institutional policies, and the subject's values and preference. The investigator must document the subject's receipt of the COVID-19 vaccine as part of collecting concomitant medication data in the eCRF.

Risk Mitigation

- The Sponsor will continue to assess whether the limitations imposed by COVID-19 or other public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

10.7. Glossary

Abbreviation/Term	Description
ACE	angiotensin-converting enzyme
ACT	Asthma Control Test
AE	adverse event
AESI	adverse event of special interest
AGREE	A working Group on ppi-REE conference
ALT	alanine aminotransferase
ARB	angiotensin-receptor blocker
AST	aspartate aminotransferase
BL	baseline
BP	blood pressure
BUN	blood urea nitrogen
C-ACT	Childhood Asthma Control Test
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CoFAR	Consortium of Food Allergy Research
CONSORT	Consolidated Standards of Reporting Trials
COVID-2019	coronavirus disease 2019
CTFG	Clinical Trial Facilitation Group
DBL	database lock
DBPCFC	double-blind, placebo-controlled food challenge
DISP	dosing instructions and symptom management plan
Dose-limiting symptoms	Any objective or subjective symptoms deemed significant per the PRACTALL guidelines (Sampson, 2012), leading to termination of DBPCFC.
EAACI	European Academy of Allergy and Clinical Immunology
EAI	epinephrine autoinjector
eCRF	electronic case report form
ED_{10}	dose needed to elicit objective symptoms in 10% of the allergic population
EEsAI	Eosinophilic Esophagitis Activity Index
EGD	esophagogastroduodenoscopy
Eliciting dose	In a DBPCFC, the dose which elicits any objective or subjective symptoms deemed significant per the PRACTALL guidelines (Sampson, 2012), leading to termination of DBPCFC.

Abbreviation/Term	Description
EoE	eosinophilic esophagitis
eos/hpf	eosinophils per high-power field
EOT	End of Treatment
EPR-3	Expert Panel Report 3
ET	Early Termination
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
FAQLQ-AF	Food Allergy Quality of Life Questionnaire–Adult Form
FAQLQ-CF	Food Allergy Quality of Life Questionnaire–Child Form
FAQLQ-PF	Food Allergy Quality of Life Questionnaire–Parent Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire–Teen Form
FEV_1	forced expiratory volume in the first second
FSH	follicle-stimulating hormone
FU	follow-up visit
FVC	forced vital capacity
GCP	Good Clinical Practice
GE	gastrointestinal eosinophilia
GERD	gastrointestinal reflux disease
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
highest tolerated dose	the highest dose a subject was able to tolerate during the updosing portion of the treatment period
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation/Term	Description
ICS	inhaled corticosteroid
ICU	intensive care unit
iDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG4	immunoglobulin G, subclass 4
IM	intramuscular
IQoL	immunotherapy-related quality of life
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LDH	lactic dehydrogenase
mApp	mobile application
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mOIT	multiple-allergen oral immunotherapy
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHLBI	National Heart, Lung, and Blood Institute
Non-qualifying Food	a Reactive Food that elicits a reaction at > 100 mg but ≤ 1000 mg during the Screening DBPCFC
Non-reactive Food	a food contained in ADP101 that has been categorized as such at Screening per Figure 3, namely one that either a) does not meet clinical history and/or ≤ 3 mm above negative control to undergo a Screening DBPCFC, or b) meets criteria to undergo a Screening DBPCFC and is tolerated through the 1000-mg dose level
NYHA	New York Heart Association
OIT	oral immunotherapy

Abbreviation/Term	Description
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PCI	potentially of clinical interest
PE	physical examination
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PEFR	peak expiratory flow rate
PFM	peak flow meter
P.O.	oral
PP	Per Protocol
PPI	proton-pump inhibitor
PRACTALL	Practical Allergy
PRO	patient-reported outcome
QoL	quality of life
QTc	corrected QT
Qualifying Food	a Reactive Food that elicits a reaction at ≤ 100 mg during the Screening DBPCFC
randomized target dose	final maintenance dose level (e.g., 1500 mg or 4500 mg) assigned at randomization
RBC	red blood cell
Reactive Food	food to which a subject has a reaction during the Screening DBPCFC; a Reactive Food is further categorized as either Qualifying or Non-qualifying.
r_s	Spearman's rank correlation coefficient
SAE	serious adverse event
SAP	statistical analysis plan
sIgE	specific immunoglobulin E
SoA	Schedule of Activities
SPT	skin-prick test
SUSAR	suspected unexpected serious adverse reaction
Th2	T helper cell
TSQM-9	9-Item Treatment Satisfaction Questionnaire for Medication
UNS	unscheduled visit
WBC	white blood cell

Abbreviation/Term	Description
WHO	World Health Organization
WOCBP	woman of childbearing potential

11. REFERENCES

Alag, A. (2019a). "Correction: Machine learning approach yields epigenetic biomarkers of food allergy: A novel 13-gene signature to diagnose clinical reactivity." PLoS One 14(7): e0220470.

Alag, A. (2019b). "Machine learning approach yields epigenetic biomarkers of food allergy: A novel 13-gene signature to diagnose clinical reactivity." PLoS One 14(6): e0218253.

Allen, K. J., Remington, B. C., Baumert, J. L., Crevel, R. W., Houben, G. F., Brooke-Taylor, S., et al. (2014). "Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications." J Allergy Clin Immunol 133(1): 156-164.

Allergen Bureau. (2019). "Summary of the 2019 VITAL Scientific Expert Panel Recommendations." from https://allergenbureau.net/wp-content/uploads/2019/09/VSEP-2019-Summary-Recommendations_FINAL_Sept2019.pdf.

Anagnostou, K., Islam, S., King, Y., Foley, L., Pasea, L., Bond, S., et al. (2014). "Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial." Lancet (London, England) 383(9925): 1297-1304.

Andorf, S., Manohar, M., Dominguez, T., Block, W., Tupa, D., Kshirsagar, R. A., et al. (2017). "Feasibility of sustained response through long-term dosing in food allergy immunotherapy." Allergy Asthma Clin Immunol 13: 52.

Andorf, S., Purington, N., Block, W. M., Long, A. J., Tupa, D., Brittain, E., et al. (2018). "Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial." Lancet Gastroenterol Hepatol 3(2): 85-94.

Andorf, S., Purington, N., Kumar, D., Long, A., O'Laughlin, K. L., Sicherer, S., et al. (2019). "A Phase 2 Randomized Controlled Multisite Study Using Omalizumab-facilitated Rapid Desensitization to Test Continued vs Discontinued Dosing in Multifood Allergic Individuals." EClinicalMedicine 7: 27-38.

Antolin-Amerigo, D., Manso, L., Caminati, M., de la Hoz Caballer, B., Cerecedo, I., Muriel, A., et al. (2016). "Quality of life in patients with food allergy." Clin Mol Allergy 14: 4.

Atkinson, M. J., Sinha, A., Hass, S. L., Colman, S. S., Kumar, R. N., Brod, M., et al. (2004). "Validation of a general measure of treatment satisfaction, the Treatment Satisfaction

Questionnaire for Medication (TSQM), using a national panel study of chronic disease." Health Qual Life Outcomes 2: 12.

Australian Government (2020). COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors. Department of Health and National Health and Medical Research Council. from https://www1.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials.

Banker, A., Bell, C., Gupta-Malhotra, M. and Samuels, J. (2016). "Blood pressure percentile charts to identify high or low blood pressure in children." BMC pediatrics 16: 98-98.

Baumert, J. L., Taylor, S. L. and Koppelman, S. J. (2018). "Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy." J Allergy Clin Immunol Pract 6(2): 457-465 e454.

Begin, P., Dominguez, T., Wilson, S. P., Bacal, L., Mehrotra, A., Kausch, B., et al. (2014a). "Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab." Allergy Asthma Clin Immunol 10(1): 7.

Begin, P., Winterroth, L. C., Dominguez, T., Wilson, S. P., Bacal, L., Mehrotra, A., et al. (2014b). "Safety and feasibility of oral immunotherapy to multiple allergens for food allergy." Allergy Asthma Clin Immunol 10(1): 1.

Bharmal, M., Payne, K., Atkinson, M. J., Desrosiers, M. P., Morisky, D. E. and Gemmen, E. (2009). "Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications." Health Qual Life Outcomes 7: 36.

Bime, C., Gerald, J. K., Wei, C. Y., Holbrook, J. T., Teague, W. G., Wise, R. A., et al. (2016). "Measurement characteristics of the childhood Asthma-Control Test and a shortened, child-only version." NPJ Prim Care Respir Med 26: 16075.

Bird, J. A., Spergel, J. M., Jones, S. M., Rachid, R., Assa'ad, A. H., Wang, J., et al. (2018). "Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial." J Allergy Clin Immunol Pract 6(2): 476-485 e473.

Blumchen, K., Trendelenburg, V., Ahrens, F., Gruebl, A., Hamelmann, E., Hansen, G., et al. (2019). "Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy." J Allergy Clin Immunol Pract 7(2): 479-491 e410.

Boyce, J. A., Assa'ad, A., Burks, A. W., Jones, S. M., Sampson, H. A., Wood, R. A., et al. (2010). "Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel." J Allergy Clin Immunol 126(6 Suppl): S1-58.

Branum, A. M. and Lukacs, S. L. (2008). "Food allergy among U.S. children: trends in prevalence and hospitalizations." NCHS Data Brief(10): 1-8.

Brough, H. A., Caubet, J. C., Mazon, A., Haddad, D., Bergmann, M. M., Wassenberg, J., et al. (2020). "Defining challenge-proven coexistent nut and sesame seed allergy: A prospective multicenter European study." J Allergy Clin Immunol 145(4): 1231-1239.

Burks, A. W., Jones, S. M., Wood, R. A., Fleischer, D. M., Sicherer, S. H., Lindblad, R. W., et al. (2012). "Oral immunotherapy for treatment of egg allergy in children." N Engl J Med 367(3): 233-243.

Caminiti, L., Pajno, G. B., Crisafulli, G., Chiera, F., Collura, M., Panasci, G., et al. (2015). "Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo-Controlled Study, with Postdesensitization Follow-Up." J Allergy Clin Immunol Pract 3(4): 532-539.

Carr, S., Chan, E. S. and Watson, W. (2018). "Eosinophilic esophagitis." Allergy, Asthma & Clinical Immunology 14(2): 58.

Cherkaoui, S., Ben-Shoshan, M., Alizadehfar, R., Asai, Y., Chan, E., Cheuk, S., et al. (2015). "Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy." Clinical and Translational Allergy 5(1): 16.

Chinthrajah, R. S., Purington, N., Andorf, S., Long, A., O'Laughlin, K. L., Lyu, S. C., et al. (2019). "Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study." The Lancet 394(10207): 1437-1449.

Coffman, A., Brooks, C., Erwin, E. and Mikhail, I. (2015). "Accidental Exposures to Known Food Allergens: Lessons from Pediatric Emergency Departments and Urgent Care Centers." Journal of Allergy and Clinical Immunology 135(2): AB251.

Cohen, B. L., Noone, S., Munoz-Furlong, A. and Sicherer, S. H. (2004). "Development of a questionnaire to measure quality of life in families with a child with food allergy." J Allergy Clin Immunol 114(5): 1159-1163.

Dellon, E. S., Liacouras, C. A., Molina-Infante, J., Furuta, G. T., Spergel, J. M., Zevit, N., et al. (2018). "Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference." Gastroenterology 155(4): 1022-1033 e1010.

Dickinson, D. F. (2005). "The normal ECG in childhood and adolescence." Heart 91(12): 1626-1630.

Du Toit, G., Sayre, P. H., Roberts, G., Lawson, K., Sever, M. L., Bahnson, H. T., et al. (2018). "Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort." J Allergy Clin Immunol 141(4): 1343-1353.

DunnGalvin, A., Cullinane, C., Daly, D. A., Flokstra-de Blok, B. M., Dubois, A. E. and Hourihane, J. O. (2010). "Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges." Clin Exp Allergy 40(3): 476-485.

Echeverria-Zudaire, L. A., Fernandez-Fernandez, S., Rayo-Fernandez, A., Munoz-Archidona, C. and Checa-Rodriguez, R. (2016). "Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy." Allergol Immunopathol (Madr) 44(6): 531-536.

Elizur, A., Appel, M. Y., Nachshon, L., Levy, M. B., Epstein-Rigbi, N., Pontoppidan, B., et al. (2019). "Walnut oral immunotherapy for desensitisation of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study." Lancet Child Adolesc Health 3(5): 312-321.

EMA (April 2020). Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic, version 3, released 28 April 2020. Agency, E. M., from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

Escudero, C., Rodriguez Del Rio, P., Sanchez-Garcia, S., Perez-Rangel, I., Perez-Farinos, N., Garcia-Fernandez, C., et al. (2015). "Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children." Clin Exp Allergy 45(12): 1833-1843.

Farrow, C. and Blissett, J. (2012). "Stability and continuity of parentally reported child eating behaviours and feeding practices from 2 to 5 years of age." Appetite 58(1): 151-156.

Fauquert, J. L., Michaud, E., Pereira, B., Bernard, L., Gourdon-Dubois, N., Rouzaire, P. O., et al. (2018). "Peanut gastrointestinal delivery oral immunotherapy in adolescents: Results of the build-up phase of a randomized, double-blind, placebo-controlled trial (PITA study)." Clin Exp Allergy 48(7): 862-874.

FDA (2017). Food Facts: Food Allergies: what you need to know. US Department of Health and Human Services. from https://www.fda.gov/downloads/Food/ResourcesForYou/Consumers/UCM220117.pdf.

FDA (March 2020). FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators and Institutional Review Boards. Updated January 27, 2021. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). from https://www.fda.gov/media/136238/download.

Feehley, T., Plunkett, C. H., Bao, R., Choi Hong, S. M., Culleen, E., Belda-Ferre, P., et al. (2019). "Healthy infants harbor intestinal bacteria that protect against food allergy." Nat Med 25(3): 448-453.

Ferreira, C. T., Vieira, M. C., Furuta, G. T., Barros, F. and Chehade, M. (2019). "Eosinophilic esophagitis-Where are we today?" J Pediatr (Rio J) 95(3): 275-281.

Feuille, E. and Nowak-Wegrzyn, A. (2016). "Oral Immunotherapy for Food Allergies." Ann Nutr Metab 68 Suppl 1: 19-31.

Flokstra-de Blok, B. M., van der Meulen, G. N., DunnGalvin, A., Vlieg-Boerstra, B. J., Oude Elberink, J. N., Duiverman, E. J., et al. (2009). "Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form." Allergy 64(8): 1209-1217.

Food Allergy Research and Education. (2018). "Food allergy & anaphylaxis emergency care plan form." from https://www.foodallergy.org/life-with-food-allergies/food-allergy-anaphylaxis-emergency-care-plan.

Food Allergy Research and Education. (2020). "Revised Anaphylaxis Management Algorithm During COVID Pandemic." from https://www.foodallergy.org/resources/home-management-anaphylaxis-during-covid-19-pandemic.

Gomez Torrijos, E., Mendez Diaz, Y., Moreno Lozano, L., Extremera Ortega, A. M., Borja Segade, J., Feo Brito, J. F., et al. (2017). "Frequency and Course of Eosinophilic Esophagitis During Oral Immunotherapy for Cow's Milk Allergy in a Series of 57 Children." J Investig Allergol Clin Immunol 27(2): 132-133.

Gupta, R. S., Warren, C. M., Smith, B. M., Blumenstock, J. A., Jiang, J., Davis, M. M., et al. (2018). "The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States." Pediatrics 142(6).

Gupta, R. S., Warren, C. M., Smith, B. M., Jiang, J., Blumenstock, J. A., Davis, M. M., et al. (2019). "Prevalence and Severity of Food Allergies Among US Adults." JAMA Netw Open 2(1): e185630.

Health Canada (03 April 2020). Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors. from https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html.

Hill, D. A., Dudley, J. W. and Spergel, J. M. (2017). "The Prevalence of Eosinophilic Esophagitis in Pediatric Patients with IgE-Mediated Food Allergy." J Allergy Clin Immunol Pract 5(2): 369-375.

Hise, K. (2020). BLA Clinical Review Memorandum for Palforzia (STN 125696). from https://www.fda.gov/media/135488/download.

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

Howe, L. C., Leibowitz, K. A., Perry, M. A., Bitler, J. M., Block, W., Kaptchuk, T. J., et al. (2019). "Changing Patient Mindsets about Non-Life-Threatening Symptoms during Oral Immunotherapy: A Randomized Clinical Trial." J Allergy Clin Immunol Pract 7(5): 1550-1559.

Ibanez, M. D., Escudero, C., Sanchez-Garcia, S. and Rodriguez del Rio, P. (2015). "Comprehensive Review of Current Knowledge on Egg Oral Immunotherapy." J Investig Allergol Clin Immunol 25(5): 316-328; quiz 312 p following 328.

Jones, S. M. and Burks, A. W. (2017a). "Food Allergy." N Engl J Med 377(12): 1168-1176.

Jones, S. M., Sicherer, S. H., Burks, A. W., Leung, D. Y. M., Lindblad, R. W., Dawson, P., et al. (2017b). "Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults." Journal of Allergy and Clinical Immunology 139(4): 1242-1252.e1249.

Kapoor, S., Roberts, G., Bynoe, Y., Gaughan, M., Habibi, P. and Lack, G. (2004). "Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions." Allergy 59(2): 185-191.

Knibb, R. C. and Stalker, C. (2013). "Validation of the Food Allergy Quality of Life-Parental Burden Questionnaire in the UK." Qual Life Res 22(7): 1841-1849.

Leung, T. F., Yung, E., Wong, Y. S., Li, C. Y. and Wong, G. W. (2009). "Quality-of-life assessment in Chinese families with food-allergic children." Clin Exp Allergy 39(6): 890-896.

Liu, A. H., Zeiger, R., Sorkness, C., Mahr, T., Ostrom, N., Burgess, S., et al. (2007). "Development and cross-sectional validation of the Childhood Asthma Control Test." J Allergy Clin Immunol 119(4): 817-825.

Maloney, J. M., Rudengren, M., Ahlstedt, S., Bock, S. A. and Sampson, H. A. (2008). "The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy." J Allergy Clin Immunol 122(1): 145-151.

Martin, L. J., Franciosi, J. P., Collins, M. H., Abonia, J. P., Lee, J. J., Hommel, K. A., et al. (2015). "Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease." J Allergy Clin Immunol 135(6): 1519-1528 e1518.

MHRA (22 April 2020). Guidance: Managing clinical trials during Coronavirus (COVID-19). from https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19.

Morais Silva, P., Antunes, J., Chambel, M., Prates, S. and Leiria Pinto, P. (2014). "Diagnosis of eosinophilic esophagitis in an infant undergoing milk oral immunotherapy - a case report." Eur Ann Allergy Clin Immunol 46(4): 154-156.

Morou, Z., Tatsioni, A., Dimoliatis, I. D. and Papadopoulos, N. G. (2014). "Health-related quality of life in children with food allergy and their parents: a systematic review of the literature." J Investig Allergol Clin Immunol 24(6): 382-395.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., et al. (2015). "Heart disease and stroke statistics--2015 update: a report from the American Heart Association." Circulation 131(4): e29-322.

Muraro, A., Roberts, G., Worm, M., Bilò, M. B., Brockow, K., Rivas, M., et al. (2014). "Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology." Allergy 69.

Narisety, S. D., Frischmeyer-Guerrerio, P. A., Keet, C. A., Gorelik, M., Schroeder, J., Hamilton, R. G., et al. (2015). "A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy." J Allergy Clin Immunol 135(5): 1275-1282.e1271-1276.

National Asthma Education Prevention Program (2007). "Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007." J Allergy Clin Immunol 120(5 Suppl): S94-138.

Noorbakhsh, R., Mortazavi, S. A., Sankian, M., Shahidi, F., Tehrani, M., Azad, F. J., et al. (2011). "Pistachio allergy-prevalence and in vitro cross-reactivity with other nuts." Allergol Int 60(4): 425-432.

Nurmatov, U., Devereux, G., Worth, A., Healy, L. and Sheikh, A. (2014). "Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis." Br J Nutr 111(1): 12-22.

PALFORZIA Package Insert (2020). from https://www.fda.gov/media/134838/download.

Purington, N., Chinthrajah, R. S., Long, A., Sindher, S., Andorf, S., O'Laughlin, K., et al. (2018). "Eliciting Dose and Safety Outcomes From a Large Dataset of Standardized Multiple Food Challenges." Front Immunol 9: 2057.

Remington, B. (2013). "Risk assessment of trace and undeclared allergens in processed foods. Dissertations, Theses, & Student Research in Food Science and Technology. 32." http://digitalcommons.unl.edu/foodscidiss/32.

Remington, B. C., Westerhout, J., Meima, M. Y., Blom, W. M., Kruizinga, A. G., Wheeler, M. W., et al. (2020). "Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens." Food Chem Toxicol 139: 111259.

Renz, H., Allen, K. J., Sicherer, S. H., Sampson, H. A., Lack, G., Beyer, K., et al. (2018). "Food allergy." Nat Rev Dis Primers 4: 17098.

Richards, S. and Tang, M. (2015). "Pharmacological management of acute food-allergic reactions." Chem Immunol Allergy 101: 96-105.

Sampson, H. A. (2001). "Utility of food-specific IgE concentrations in predicting symptomatic food allergy." J Allergy Clin Immunol 107(5): 891-896.

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.

Sampson, H. A., Munoz-Furlong, A., Campbell, R. L., Adkinson, N. F., Jr., Bock, S. A., Branum, A., et al. (2006). "Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." J Allergy Clin Immunol 117(2): 391-397.

Sanchez-Garcia, S., Rodriguez Del Rio, P., Escudero, C., Martinez-Gomez, M. J. and Ibanez, M. D. (2012). "Possible eosinophilic esophagitis induced by milk oral immunotherapy." J Allergy Clin Immunol 129(4): 1155-1157.

Savvatianos, S., Konstantinopoulos, A. P., Borga, A., Stavroulakis, G., Lidholm, J., Borres, M. P., et al. (2015). "Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children." J Allergy Clin Immunol 136(1): 192-194.

Schatz, M., Sorkness, C. A., Li, J. T., Marcus, P., Murray, J. J., Nathan, R. A., et al. (2006). "Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists." J Allergy Clin Immunol 117(3): 549-556.

Schoepfer, A. M., Straumann, A., Panczak, R., Coslovsky, M., Kuehni, C. E., Maurer, E., et al. (2014). "Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis." Gastroenterology 147(6): 1255-1266 e1221.

Shaker, M. S., Schwartz, J. and Ferguson, M. (2017). "An update on the impact of food allergy on anxiety and quality of life." Curr Opin Pediatr 29(4): 497-502.

Sicherer, S. H. and Sampson, H. A. (2014). "Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment." J Allergy Clin Immunol 133(2): 291-307; quiz 308.

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

Staden, U., Rolinck-Werninghaus, C., Brewe, F., Wahn, U., Niggemann, B. and Beyer, K. (2007). "Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction." Allergy 62(11): 1261-1269.

Tang, M. L., Ponsonby, A. L., Orsini, F., Tey, D., Robinson, M., Su, E. L., et al. (2015). "Administration of a probiotic with peanut oral immunotherapy: A randomized trial." J Allergy Clin Immunol 135(3): 737-744.e738.

Uotila, R., Kukkonen, A. K., Greco, D., Pelkonen, A. S. and Mäkelä, M. J. (2017). "Peanut oral immunotherapy decreases IgE to Ara h 2 and Ara h 6 but does not enhance sensitization to cross-reactive allergens." J Allergy Clin Immunol 139(4): 1393-1396.e1396.

Uotila, R., Kukkonen, A. K., Pelkonen, A. S. and Mäkelä, M. J. (2016). "Cross-sensitization profiles of edible nuts in a birch-endemic area." Allergy 71(4): 514-521.

Urbano, F. L. (2008). "Review of the NAEPP 2007 Expert Panel Report (EPR-3) on Asthma Diagnosis and Treatment Guidelines." J Manag Care Pharm 14(1): 41-49.

van der Velde, J. L., Flokstra-de Blok, B. M., Vlieg-Boerstra, B. J., Oude Elberink, J. N., Schouten, J. P., Dunngalvin, A., et al. (2009). "Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults." Qual Life Res 18(2): 245-251.

Varshney, P., Jones, S. M., Scurlock, A. M., Perry, T. T., Kemper, A., Steele, P., et al. (2011). "A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response." J Allergy Clin Immunol 127(3): 654-660.

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.

Wang, J. (2010). "Management of the patient with multiple food allergies." Curr Allergy Asthma Rep 10(4): 271-277.

Wassenberg, J., Cochard, M. M., Dunngalvin, A., Ballabeni, P., Flokstra-de Blok, B. M., Newman, C. J., et al. (2012). "Parent perceived quality of life is age-dependent in children with food allergy." Pediatr Allergy Immunol 23(5): 412-419.

Wright, B. L., Fernandez-Becker, N. Q., Kambham, N., Purington, N., Tupa, D., Zhang, W., et al. (2018). "Baseline Gastrointestinal Eosinophilia Is Common in Oral Immunotherapy Subjects With IgE-Mediated Peanut Allergy." Front Immunol 9: 2624.