Allergenic Products Advisory Committee Meeting
September 13, 2019

Peanut*, Arachis hypogaea,* Allergen Powder for Oral Administration (Proposed Trade Name: Palforzia)

Applicant:
Aimmune Therapeutics

Table of Contents

Glossary

AE	Adverse event
AESI	Adverse event of special interest
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
DBPCFC	Double-blind placebo-controlled food challenge
EoE	Eosinophilic esophagitis
FDA	Food and Drug Administration
GI	Gastrointestinal
IgE	Immunoglobulin E
IDE	Initial dose escalation
OFC	Oral food challenge
OIT	Oral immunotherapy
QoL	Quality of life
SAE	Serious adverse event

1.0 Executive Summary

A biologics license application (BLA) was submitted by Aimmune Therapeutics to the US Food and Drug Administration (FDA) for peanut (*Arachis hypogaea*) allergen powder. The proposed trade name, Palforzia, will be used in this briefing document. The candidate therapy is initially sourced as shelled, dry roasted peanut (*Arachis hypogaea*) allergen powder and is evaluated for quantities of specific allergenic peanut proteins. The proposed indication is a treatment "to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy."

The BLA includes efficacy and safety data from 7 clinical studies, including two phase 2 studies (ARC001 and ARC002) and 5 phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC011). ARC003 provided efficacy data, ARC003 and ARC007 provided pooled controlled safety data, and ARC004 and ARC011 provided additional uncontrolled safety data.

ARC003 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy and safety of Palforzia in 555 subjects 4 to 55 years of age. The majority of participants were 4 through 17 years of age (n = 499). As part of the eligibility criteria, subjects underwent a double-blind placebo-controlled food challenge (DBPCFC) prior to randomization. Subjects were randomized in a 3:1 ratio to receive Palforzia or placebo. The study includes 3 dosing phases: an initial dose escalation over 1-2 days under clinical observation, up-dosing every 2 weeks, and maintenance dosing of 300 mg Palforzia daily. The primary efficacy endpoint was the proportion of subjects 4 through 17 years of age in the intent-to-treat (ITT) population who tolerated a dose of at least 600 mg of peanut protein with no more than mild symptoms at the exit DBPCFC at the end of the maintenance period. The ARC003 success criterion was met if the lower bound of the 95% CI for the treatment difference between Palforzia and placebo was greater than 15%.

The ARC003 success criterion was met for the subject population 4 through 17 years of age with a treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3). Subjects who did not have an exit DBPCFC were analyzed as non-responders for the primary efficacy endpoint. While

discontinuations in the pediatric Palforzia group were elevated in ARC003 (Palforzia 21.4% vs placebo 8.0%), efficacy was demonstrated despite these discontinuations. A sensitivity analysis evaluating a worst-case scenario[1] continued to demonstrate a robust treatment effect.

Data in adults are presented for completeness. The efficacy evaluation in the adult ITT population, a key secondary endpoint, did not demonstrate a significant treatment difference; the efficacy estimate was 27.2 (95% CI: -1.7, 56.0). The study enrolled a small number of adults (n = 55) which the applicant states was due to recruitment issues. In addition, the substantial discontinuation rates in the adult population likely impacted the efficacy findings, with 54% of adults discontinuing from treatment. A total of 5% of the discontinuations were due to protocol-mandated dose titration failures. In a supplementary subgroup analysis of efficacy in the adult completer population (n= 33), the efficacy estimate was 69.6% (95% CI: 35.1, 100.0).

In the integrated summary of safety, two datasets were evaluated for subjects 4 through 17 years of age: the controlled safety population (N=1001; Palforzia = 709, placebo = 292) and the integrated safety population (N =812). The controlled safety population consists of comparisons between subjects who received Palforzia or placebo in the controlled phase 3 studies (ARC003 and ARC007). The integrated safety population includes any subject who received at least one dose of Palforzia in both controlled and uncontrolled studies (ARC003, ARC004, ARC007, and ARC011).

Palforzia treated subjects in the pediatric safety population reported an increased number of allergic reactions, including systemic allergic reactions, compared to placebo-treated subjects. A total of 9.4% subjects taking Palforzia had a systemic allergic reaction during initial dose escalation and up-dosing compared to 3.8% of placebo subjects. This imbalance was seen during maintenance as well with 8.7% of Palforzia treated patients having a systemic allergic reaction compared to 1.7% of placebo-treated subjects. During the maintenance period, 7.7% of Palforzia treated subjects used epinephrine compared to 3.4% in the placebo group. Twelve subjects treated with Palforzia were diagnosed with eosinophilic esophagitis (EoE) in the entire clinical development program while no subjects in the placebo group of the controlled safety population received a diagnosis of EoE. Similar safety data are seen in the adult population with respect to systemic allergic reactions.

While the primary efficacy endpoint of the phase 3 study ARC003 was met for subjects 4 through 17 years of age, the Palforzia treatment group had an increased number of discontinuations, systemic allergic reactions and reports of eosinophilic esophagitis compared to the placebo treated group, though both groups followed a peanut avoidance diet.

This Allergenic Products Advisory Committee (APAC) meeting is being convened to discuss whether efficacy and safety data support licensure of Palforzia as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients 4 through 17 years of age with a confirmed diagnosis of peanut allergy.

[1] The worst-case imputation was defined as the following: placebo-treated subjects with missing data for the exit DBPCFC were considered as responders and AR101-treated subjects with missing data for the exit DBPCFC were considered as non-responders

2.0 Background

2.1 General Product Information

Product name: Peanut, *Arachis hypogaea,* Allergen Powder

Proposed trade name: Palforzia

Proposed indication: Palforzia is indicated as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

Proposed dosage and administration: Palforzia is initially sourced as shelled, dry roasted peanut (*Arachis hypogaea*) allergen powder and is evaluated for quantities of specific allergenic peanut proteins. The drug product is filled in pull apart hydroxypropyl methyl cellulose (HPMC) capsules or filled in foil-laminate sachets and supplied in color-coded pull-apart capsules at 5 dosage strengths (0.5, 1, 10, 20, and 100 mg) and sachets at 1 dosage strength (300 mg). Product dosing begins with an initial dose escalation of 0.5 to 6 mg of Palforzia over 1 day under supervision of a qualified healthcare professional trained in the diagnosis and treatment of allergic diseases in a healthcare setting equipped to manage severe allergic reactions. Subsequently, up-dosing begins at 3 mg Palforzia and continued, as tolerated, with up-dosing every 2 weeks until reaching 300 mg daily maintenance treatment. The first dose of each new level in the up-dosing schedule and first maintenance dose, like the initial dose escalation, are administered under supervision of a qualified healthcare professional in a healthcare setting.

2.2 Epidemiology and Clinical Manifestations

Food allergy arises from a failure of the immune system to generate or maintain tolerance to specific food proteins. IgE-mediated food allergy is a deleterious immune response to food proteins characterized by acute onset of symptoms generally within 2 hours after ingestion of or exposure to the protein [1]. The clinical presentation includes a range of symptoms from oral pruritus to acute urticaria/angioedema which can progress to more serious sequelae such as anaphylaxis, hypotension, and multiple organ dysfunction syndrome [1].

The most common food allergens are peanut, tree nut, milk, egg, soy, wheat, and shellfish [2]. These foods constitute more than 90% of food allergies in children [3]. Some food allergies (milk, egg, wheat, and soy) have an increased chance of resolving with age whereas others (peanut, tree nut, and shellfish) tend to be persistent over time [4].

Food allergy affects up to 15 million people in the U.S., approximately 6 million of whom are children. Prevalence has been increasing, particularly in children; the National Center for Health Statistics reports that the prevalence increased from 3.4% in 1997-1999 to 5.1% in 2009-2011 in individuals 0 to 17 years of age [5]. Peanut allergy is often diagnosed in childhood when most food allergies develop. The prevalence of peanut allergy in children <5 years of age is estimated to be 0.75-1.3%, and in adults the prevalence is about 0.7% [3]. Only about 20% of children outgrow a peanut allergy [3].

Quality of life (QoL) in food-allergic individuals and their caregivers is often adversely affected due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods which is associated with significant anxiety [6].

Despite peanut avoidance, accidental exposures occur. Two studies estimated that accidental exposures occur at an annual incidence of 12.4% and 14.3% in peanut allergic children [7, 8]. The potential consequences of accidental exposure can be serious and life-threatening. About 50% of cases of anaphylaxis reported by emergency departments are due to a food allergen [9]. Fatalities due to anaphylaxis from food allergies are estimated at about 100 per year with most deaths occurring during early adulthood [10].

Diagnosis and Current Standard of Care

The diagnosis of food allergy is made based on patient history and IgE testing. Although an oral food challenge (OFC) may be performed to rule out food allergy or to confirm that tolerance has developed in a patient with a history of allergic symptoms, oral food challenge is not generally used to diagnose food allergy when patients have a strong clinical history with confirmatory IgE testing.

To prevent systemic allergic reactions including anaphylaxis, food-allergic individuals must maintain a strict avoidance diet. Despite these avoidance measures, accidental exposures to food allergens occur. Treatment is limited to mitigating the symptoms of allergic reactions after accidental exposure to allergens - either with immediate injection of epinephrine for suspected or confirmed anaphylaxis or with antihistamines for milder symptoms.

2.3 Regulatory Basis for Use of Oral Food Challenge

The Allergenic Products Advisory Committee (APAC) was convened on January 21, 2016 to obtain advice regarding the design of investigational protocols proposing to treat IgE-mediated food allergy and to discuss safety and efficacy endpoints, including challenge study endpoints, to support licensure of food allergy immunotherapy products. In particular, the committee was asked to comment on the use of OFC to assess of efficacy in clinical studies. The discussion included the following issues regarding the use of OFCs: objective criteria for determining the eliciting dose, particularly in children less than 5 years of age, clinically meaningful parameters including amplitude of response, safety considerations for the food challenge, approaches other than food challenge studies to demonstrate effectiveness of immunotherapy products, and specific safety monitoring for signs and symptoms of allergic reactions.

During the discussion of OFCs, the committee discussed the practical goal of immunotherapy: to induce full tolerance or diminish the risk of reactions. The committee agreed that a clinically meaningful goal of immunotherapy for the treatment of food allergy would be to diminish the risk of life-threatening allergy with accidental exposure, acknowledging that data from available studies have not shown induction of full tolerance by oral immunotherapy. Therefore, the goal of therapy would be to reduce the risk of life-threatening reactions to accidental exposures instead of allowing patients to add the culprit food to the diet ad lib. To this end, treatment would focus on increasing the dose of food ingested without a serious allergic reaction after a period of treatment. In addition, patients who have a history of life-threatening anaphylaxis are those who may benefit most from this treatment. The committee agreed that, from a research standpoint, there is no substitute for an oral challenge to determine whether or not a treatment is effective. A randomized, controlled field study (in subjects practicing allergen avoidance) where the primary endpoint would be a reduction of the rate and/or severity of reactions to accidental food exposure in the treatment arm compared to the control arm, would require large cohorts and long study durations to detect statistically significant differences.

The committee also discussed approaches to safety monitoring for signs and symptoms of allergic reactions in pediatric study subjects enrolled in clinical trials evaluating food immunotherapy products. The committee agreed that the safety of using OFCs and oral immunotherapy in food allergy studies can be strengthened by using experts in the field, e.g. those who have experience using immunotherapy and recognizing and treating allergic reactions.

The materials for the January 2016 meeting can be found at: https://www.fda.gov/advisory-committees/allergenic-products-advisory-committee/2016-meeting-materials-allergenic-products-advisory-committee

3.0 Overview of Clinical Studies

The clinical development program for Palforzia includes 7 studies (ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, and ARC011) to support the use of Palforzia in children 4-17 years of age. Four studies are complete (ARC001, ARC002, ARC003, and ARC007).

The two completed pivotal studies were ARC003, a randomized-controlled Phase 3 study that evaluated the safety and effectiveness of Palforzia in subjects 4 through 55 years of age, and ARC007, a randomized-controlled Phase 3 study that evaluated the safety of Palforzia in children 4 through 17 years of age. Unlike ARC003, ARC007 was designed to simulate clinical practice in that it did not require a positive DBPCFC to enroll in the study or require a food challenge at study end to assess efficacy. ARC007 also did not contain a maintenance phase; subjects reached the daily dose of 300 mg Palforzia and were discharged from the study. ARC001 was an early phase study to establish the preliminary safety profile and inform the efficacy assumptions for the pivotal efficacy study. ARC002 was an uncontrolled follow-on study for ARC001 and provided supplemental safety data. The remaining studies (ARC004, ARC008, and ARC011) are open-label follow-on studies. ARC004, ARC008 and ARC011 are on-going (see Table 1). Oral food challenges were not required for entry into these follow-on studies. Since adverse reactions to Palforzia in ARC003 included mild-moderate systemic allergic reactions leading to an increase in epinephrine use in the treatment arm, the FDA and the applicant agreed that the BLA would include interim safety data from ongoing studies ARC004, ARC008 and ARC011 that would be limited to serious adverse events, adverse events that led to permanent discontinuation of study product, anaphylaxis, severe treatment related adverse events and deaths. The safety data from these ongoing studies were submitted with a cut-off date July 15, 2018. Study ARC008 contains blinded safety data from study participants who were enrolled in on-going, blinded European study, ARC010 (protocol not reviewed by the FDA) and entered follow-on study ARC008 after completing ARC010; therefore, the blinded interim data from ARC008 were not included in the discussion of safety in Section 5 of this briefing document. Differences in data collection in ARC001 and ARC002 did not allow for integration into the pooled safety results in Section 5. The safety results of ARC001 and ARC002 were generally consistent with the studies described in the briefing document. These small phase 2 studies will not be discussed further.

Table 1 summarizes the studies submitted to the BLA. Sections 4 and 5 of the briefing document will discuss the efficacy and safety findings from these studies as follows:

- Section 4: Study Intended to Support Efficacy (ARC003) will describe the study design of ARC003, study population, and efficacy results.

- Section 5: Integrated Summary of Safety will discuss discontinuations due to adverse events, serious adverse events (SAEs), and adverse events of special interest (AESIs) from all studies. AESIs were specified as systemic allergic reactions including anaphylaxis and gastrointestinal (GI) adverse events including eosinophilic esophagitis (EoE).

Table 1: Summary of Clinical Studies Submitted to the Palforzia BLA STN 125696/0

Study ID *Study Dates (month/year)*	**Study Design**	**Treatment Arms (Randomization Ratio)**	**Study Endpoints**	**Treatment Duration**	**N**	**Study Population Age Range** (years)	**Countries** (number of sites)
Controlled Studies	--	--	--	--	--	--	--
ARC001 (NCT01987817) *2/14-1/15*	Phase 2, R, DB, PC, MC	300mg Palforzia daily: Placebo (1:1)	Safety, Ingestion* of 300mg peanut protein at exit DBPCPC	6 months	56	4-26	US (8)
ARC003 (NCT02635776) *12/15-1/16*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (3:1)	Safety, Ingestion* of 600mg peanut protein at exit DBPCFC	12 months	555	4-55	NA (51), EU (15)
ARC007 (NCT03126227) *5/17-8/18*	Phase 3, R, DB, PC, MC No entry DBPCFC or maintenance phase	300mg Palforzia daily: Placebo (2:1)	Safety	6 months	506	4-17	US (59), CA (5)
Uncontrolled Follow—On Studies	--	--	--	--	--	--	--
ARC002 (NCT02198664) *8/14-1/18*	Phase 2, OL, MC, follow-on for ARC001	300mg Palforzia or 2000mg Palforzia daily	Safety	2.7 years	47	4-26	US (8)
ARC004 (NCT02993107) *Ongoing*	Phase 3, OL, follow-on for ARC003	300mg Palforzia daily, QOD, BIW, QW, or QOW	Safety	3 years	388	4-55	NA (51), EU (13)
ARC008 (NCT03292484) *Ongoing*	Phase 3, OL, follow-on for all Palforzia studies	300mg Palforzia daily, QOD, BIW, QW, or QOW	Safety	3 years	360	4-55	US (61), CA (5), EU (18)
ARC011 (NCT03337542) *Ongoing*	Phase 3, OL, follow-on for ARC007	300mg Palforzia daily	Safety	6 months	237	4-17	NA (63)

**Ingestion of peanut protein during DBPCFC with no more than minimal allergic symptoms, N = number of subjects, R = randomized, DB = double-blind, PC = placebo-controlled, OL = open label, MC = multicenter, US = United States of America, CA=Canada, NA = North America, EU = Europe, DBPCFC = double-blind placebo-controlled food challenge, QOD = over other day, BIW = biweekly, QW = weekly, QOW = every other week*

4.0 Study Intended to Support Efficacy (ARC003)

4.1 ARC003 Study Design

Study Title:
Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE)

Study Design:
ARC003 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted at 66 sites. Fifty-one investigational sites in North America enrolled 78.9% percent of the population. The total study population consisted of 555 subjects 4 to 55 years of age. There were 499 individuals 4 through 17 years of age in this study. Restriction of the efficacy analysis to the pediatric population was pre-specified in a protocol amendment prior to study unblinding due to low enrollment of adult subjects. Subjects were randomized in a 3:1 ratio to receive treatment or placebo and randomization was stratified by geographic region (North American and Europe) was well as by age (children 4 through 17 years of age and adults 18 to 55 years of age).

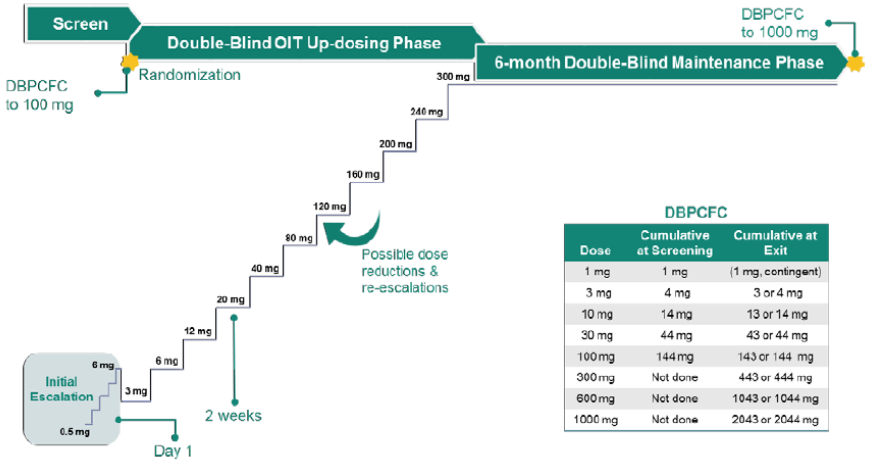
Peanut-allergic subjects 4-55 years of age with positive peanut-specific serum IgE or skin prick testing, were screened for study eligibility. Subjects with uncontrolled or severe asthma, a history of EoE, severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of the screening were excluded from the study.

Prior to randomization, subjects underwent a screening DBPCFC with up to 100 mg peanut protein and placebo to confirm true peanut allergy. Subjects who did not develop dose-limiting symptoms to 100 mg of peanut protein were not randomized to receive a study treatment. Dose-limiting symptoms (e.g., skin, respiratory, gastrointestinal, cardiovascular, and neurologic symptoms) were evaluated by a blinded physician and graded for severity based on the Consortium of Food Allergy Research (CoFAR) grading system for allergic reactions [12]. A copy of this grading scale can be found in Section 5.3, Table 11 of this briefing package.

After randomization, dosing began under supervision in clinic with an initial dose escalation of 0.5 to 6 mg peanut protein or placebo over 2 days. Subsequently, subjects began dosing at 3 mg Palforzia or placebo and continued, as tolerated, with up-dosing every 2 weeks (20-40 weeks) until reaching 300 mg maintenance treatment. Maintenance therapy was continued for a minimum of 24 weeks; however, some subjects took therapy for 28 weeks to account for dose reductions and re-escalations. Each new step in the up-dosing procedure was administered in a clinic setting with personnel trained to treat allergic reactions. Subjects were continually assessed for allergic symptoms throughout the treatment duration by electronic diary cards, clinic visits, and telephone contact. Allergic symptoms were assessed by the investigator using definitions consistent with the PRACTALL consensus report on DBPCFCs and the CoFAR grading system for allergic reactions [10, 12]. Dose modifications or discontinuation from study treatment were made per investigator discretion based on these assessments. Study participants were reminded to avoid peanut at each study visit.

The efficacy assessment for the primary endpoint was a DBPCFC performed at the end of the maintenance period for subjects who were able to ingest 300 mg daily of Palforzia for 24 weeks. Single doses of 3, 10, 30, 100, 300, 600, and 1000 mg peanut protein (2043 mg cumulative) or placebo given at 20-30 minute intervals were evaluated in the exit DBPCFC. Investigators were

provided with a standardized oral food challenge protocol to ensure each challenge was conducted in an analogous manner at each study site. Please see Figure 1 below for an illustration of this procedure. Subjects were considered treatment responders for the primary endpoint if 600 mg of peanut protein was ingested with no or only mild symptoms. Similar to dose-escalation procedures, mild symptoms were defined using the CoFAR grading scale (Please see Table 11 in Section 5.3 for these criteria).



DBPCFC

Dose	Cumulative at Screening	Cumulative at Exit
1 mg	1 mg	(1 mg, contingent)
3 mg	4 mg	3 or 4 mg
10 mg	14 mg	13 or 14 mg
30 mg	44 mg	43 or 44 mg
100 mg	144 mg	143 or 144 mg
300 mg	Not done	443 or 444 mg
600 mg	Not done	1043 or 1044 mg
1000 mg	Not done	2043 or 2044 mg

Figure 1: Overview of ARC003 Study Design. Adapted from STN125696/0, Clinical Study Report ARC003

Study Endpoints:

Primary Endpoint: The primary efficacy endpoint was the proportion of subjects 4 through 17 years of age who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. Subjects who tolerated 600 mg were considered responders for the primary efficacy endpoint. Subjects who did not have an Exit DBPCFC were considered non-responders for the purpose of this analysis. The point estimate of the primary efficacy endpoint was the difference in responder proportions between treatment groups (Palforzia – placebo). The pre-specified criterion for study success was demonstrated if the lower bound of the corresponding 95% CI of the difference of response rates was greater than 15%.

Key Secondary Endpoints:

1. The proportion of subjects 4 through 17 years of age who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
2. The proportion of subjects 4 through 17 years of age who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
3. The maximum severity of symptoms (none, mild, moderate, or sever or higher) subjects 4 through 17 years of age occurring at any challenge dose of peanut protein during the Exit DBPCFC
4. The proportion of subjects 18 to 55 years of age who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

Safety Endpoints:

1. Frequencies of adverse events (AEs) including serious adverse events (SAEs) in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
2. Frequency of epinephrine use as a rescue medication during OIT (Initial Escalation, Up-dosing, and maintenance Periods) in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
3. Frequency of anaphylaxis during OIT (Initial Escalation, Up-dosing, and maintenance Periods) in in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
4. Frequency of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the maintenance Period, normalized for duration of treatment in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
5. Frequency of accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
6. Severity of adverse events associated with accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
7. Frequency of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive
8. Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma in the following 5 age groups: 4 through 17, 4 to 11, 12 to 17, 18 to 55, and 4 to 55 years of age, inclusive

Selected Analysis Populations:

Intent-to-Treat (ITT)

This population serves as the primary analysis population for the evaluation of efficacy data. It consists of all randomized subjects who received at least one dose of randomized study treatment.

Completer Population

The Completer population includes all subjects in the ITT population who completed treatment and have an evaluable Exit DBPCFC. An evaluable Exit DBPCFC is defined as completion of at least the peanut part of the food challenge. Sensitivity analyses, supportive analyses of the primary endpoint, key secondary endpoints, and other secondary endpoints using the Completer population are presented and analyzed where relevant.

Per Protocol (PP) Population

The Per Protocol (PP) population is a subset of the Completer population limited to subjects with no major protocol deviations.

4.2 ARC003 Demographics

Tables 2 and 3 show the demographic characteristics of participants in study ARC003. More males than females participated in the studies. Most of the participants were white and resided in North America. These trends were noted in both the Palforzia and placebo populations with no major imbalances between the treatment groups identified. Table 3 shows the demographic characteristics in adult participants. This latter group enrolled a relatively higher proportion of subjects from Europe, but the demographic breakdown was otherwise similar.

The majority of subjects had a food allergy other than peanut (65.5%). Other common atopic conditions included allergic rhinitis (71.8%), asthma (52.8%), and atopic dermatitis (62.1%). These conditions, which were balanced across treatment groups, are expected co-morbidities in peanut allergic subjects.

Table 2: Demographic Characteristics of Randomized Pediatric Subjects 4 through 17 Years of Age (ITT population): Study ARC003

	Palforzia N(%)	Placebo N(%)	Total N(%)
Number of subjects	372	124	496
Gender:	--	--	--
Male	208 (55.9)	76 (61.3)	284 (57.3)
Female	164 (44.1)	48 (38.7)	212 (42.7)
Age (years):	--	--	--
4 to 11	238 (64.0)	89 (71.8)	327 (65.9)
12 to <18	134 (36.0)	35 (28.2)	169 (34.1)
Race			
White	292 (78.5)	97 (78.2)	389 (78.4)
Black or African American	6 (1.6)	3 (2.4)	9 (1.8)
Asian	41 (11.0)	8 (6.5)	49 (9.9)
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.2)
Other	31 (8.3)	16 (12.9)	47 (9.5)
Ethnicity	--	--	--
Hispanic or Latino	29 (7.8)	15 (12.1)	44 (8.9)
Not Hispanic or Latino	343 (92.2)	109 (87.9)	452 (91.1)
Geographic Region	--	--	--
North America	302 (81.2)	100 (80.6)	402 (81.0)
Europe	70 (18.8)	24 (19.4)	94 (19.0)

Adapted from 125696/0: Clinical Study Report ARC003, Table 15

N= number of subjects

Table 3: Demographic Characteristics of Randomized Adult Subjects 18 to 55 Years of Age (ITT population): Study ARC003

	Palforzia N (%)	Placebo N(%)	Total N(%)
Number of subjects	41	14	55
Median age (years)	24.0	22.0	23.0
Gender:			
Male	25 (61.0)	6 (42.9)	31 (56.4)
Female	16 (39.0)	8 (57.1)	24 (43.6)
Race	--	--	--
White	37 (90.2)	12 (85.7)	49 (89.1)
Black or African American	0	0	0
Asian	3 (7.3)	2 (14.3)	5 (9.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (2.4)	0	1 (1.8)
Ethnicity	--	--	--
Hispanic or Latino	1 (2.4)	2 (14.3)	3 (5.5)
Not Hispanic or Latino	40 (97.6)	12 (85.7)	52 (94.5)
Geographic Region	--	--	--
North America	24 (58.5)	9 (64.3)	33 (60.0)
Europe	17 (41.5)	5 (35.7)	22 (40.0)

Adapted from 125696/0: Clinical Study Report ARC003, Table 14.1.3.9

N= number of subjects

Table 4 displays the subject disposition and analysis groups used to evaluate the primary and key secondary efficacy endpoints. Among children 4 through 17 years of age, 21.4% of subjects treated with Palforzia discontinued compared to 8.0% of placebo recipients. Reasons for discontinuation of Palforzia included adverse events (9.1%) and withdrawal of consent (8.3%). A total of 1.1% were withdrawn due to dosing failures in each of the up-titration and maintenance dosing periods as mandated by the protocol. In the placebo group, 8% of subjects discontinued with the most common reason being withdrawal of consent. Withdrawal due to adverse events accounted for 1.6% of the withdrawals, and no subjects were withdrawn due to dosing failures (see Table 4).

Table 4: Subject Disposition by Age Group: Study ARC003

Disposition	Palforzia N (%)	Placebo N (%)	Total N (%)
Study Disposition (4 through 17 years of age):	--	--	--
Randomized	374	125	499
Treated	372	124	496
ITT[1]	372 (99.5)	124 (99.2)	496 (99.4)
PP	289 (77.3)	113 (90.4)	402 (80.6)
Completer	296 (79.1)	116 (92.8)	412 (82.6)
Discontinued[2]	80 (21.4)	10 (8.0)	90 (18.0)
Adverse event	34 (9.1)	2 (1.6)	36 (7.2)
Withdrew consent	31 (8.3)	6 (4.8)	37 (7.4)
Initial dose escalation failure	4 (1.1)	1 (0.8)	5 (1.0)
Up-dosing failure	4 (1.1)	0	4 (0.8)
maintenance dose failure	1 (0.3)	0	1 (0.2)
Investigator decision	1 (0.3)	0	1 (0.2)
Other[3]	5 (1.3)	1 (0.8)	6 (1.2)
Study Disposition (18 through 55 years of age):	--	--	--
Randomized	42	14	56
Treated	41	14	55
ITT[4]	41 (97.6)	14 (100.0)	55 (98.2)
PP	20 (47.6)	13 (92.9)	33 (58.9)
Completer	20 (47.6)	13 (92.9)	33 (58.9
Safety	41 (97.6)	14 (100.0)	55 (98.2)
Discontinued[2]	--	--	--
Adverse event	6 (14.3)	0	6 (10.7)
Withdrew consent	10 (23.8)	1 (7.1)	11 (19.6)
Initial dose escalation failure	0	0	0
Up-dosing failure	2 (4.8)	0	2 (3.6)
Maintenance dose failure	0	0	0
Investigator decision	0	0	0
Other[5]	4 (9.5)	0	4 (7.1)

Adapted from 125696/0: Clinical Study Report ARC003, Table14, Figure 2 & 3
N = number of subjects
[1]Two subjects did not receive Palforzia; 1 withdrew consent, 1 was a randomization error. One subject in the placebo group withdrew consent
[2]Percentage calculated from number of subjects randomized into each arm
[3]In the Palforzia group the reasons listed for "other" are: non-compliance (2), relocation (1), schedule conflict (1), and randomized in error (1). In the placebo group one subject discontinued due to relocation
[4] One subject no longer met eligibility criteria
[5]In the Palforzia group the reasons listed for "other" are: lost to follow-up (2), no longer met eligibility criteria (1), unable to tolerate smell/taste of study product (1)

4.3 ARC003 Efficacy Results

Primary Efficacy Results:

The study met the pre-specified success criterion for efficacy as shown in Table 5.

Table 5: Efficacy Analysis of the Primary Endpoint in the Intent-To-Treat (ITT) population in Subjects 4 through 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)*	P-value
Palforzia	372	67.2 (62.3, 71.8)	63.2 (53.0, 73.3)	<0.0001
Placebo	124	4.0 (1.7, 9.1)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 23
N = number of subjects
*The pre-specified success criterion for efficacy was demonstrated if the lower bound of the 95% CI was greater than 15%.
CI=confidence interval

To supplement this analysis, a worst-case scenario analysis was performed where placebo subjects with no evaluable exit food challenge were treated as responders, resulting in an estimated treatment effect of 56.7% (95% CI:46.6, 66.9).

Key Secondary Efficacy Results:

Tables 6 through 9 display the analyses of the key secondary efficacy endpoints. These endpoints were tested sequentially, and the success criterion was met for the first 3 key secondary endpoints, but not for the last key secondary efficacy endpoint in the adult population (subjects 18-55 years of age).

The first 3 key secondary endpoints demonstrate a consistent dose-response relationship in the pediatric population at oral challenge doses of 300mg and 1000mg. In addition, for any dose ingested during the exit DBPCFC, subjects treated with Palforzia reported less severe symptoms overall when compared to the placebo population.

Table 6: Secondary Efficacy Analysis of the Proportion of Subjects who Ingested 300mg of Peanut Protein at the Exit DBPCFC in the ITT Population 4 through 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	372	76.6 (72.1, 80.6)	68.5 (58.6, 78.5)	<0.0001
Placebo	124	8.1 (4.4, 14.2)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29
N = number of subjects

Table 7: Secondary Efficacy Analysis of the Proportion of Subjects who Ingested 1000mg of Peanut Protein at the Exit DBPCFC in the ITT Population 4 through 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	372	50.3 (45.2, 55.3)	47.8 (38.0, 57.7)	< 0.0001
Placebo	124	2.4 (0.8, 6.9)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29
N = number of subjects

Table 8: Secondary Efficacy Analysis of the Maximum Severity of Symptoms at any Challenge Dose of Peanut Protein during the Exit DBPCFC in the ITT Population 4 through 17 Years of Age: Study ARC003

Treatment	N	None	Mild	Moderate	Severe or higher[1]	P-value[2]
Palforzia N (% of total)	372	140 (37.6)	119 (32.0)	94 (25.3)	19 (5.1)	<0.0001
Placebo N (% of total)	124	3 (2.4)	35 (28.2)	73 (58.9)	13 (10.5)	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29
N = number of subjects
[1] Includes severe symptoms, life-threatening or fatal reactions. No subjects had symptoms considered life-threatening or fatal
[2]Treatment difference was tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region (North America, Europe)

The prespecified success criterion was not met in the analysis in adults which was limited due to the small sample size and failed to meet the specified success criterion (Table 9). A supplementary analysis of the adult completer population demonstrated a treatment difference of 69.6 (95% CI: 35.1, 100.0). Overall Type I error rate was not controlled for this supplementary analysis because this analysis is a sensitivity analysis and descriptive in nature.

Table 9: Secondary Efficacy Analysis of the Proportion of Subjects who Ingested 600mg of peanut protein at the Exit DBPCFC in the ITT Population 18 to 55 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	41	41.5 (27.8, 56.6)	27.2 (-1.7, 56.0)	0.0648
Placebo	14	14.3 (4.0, 39.9)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29

5.0 Integrated Summary of Safety

5.1 Methodology

To assess the overall safety profile of Palforzia in the age group intended for use, a pool of subjects 4 through 17 years of age from controlled (ARC003 and ARC007) and uncontrolled studies (ARC004 and ARC011) was analyzed. This dataset is presented in two groups for the Phase 3 study program: the controlled safety population and the integrated safety population. These datasets were integrated because the study procedures including initial dose escalation, up-dosing, and maintenance as well as safety data collection and reporting were consistent for the phase 3 studies and therefore allowed for integration. The demographic distribution was similar in studies ARC003 and ARC007 in terms of sex and race and ethnicity: participants in either study or treatment assignment were mostly white non-Hispanic or Latino males. Please see Section 5.4 for further discussion on the allergic characteristics of the controlled safety population.

The controlled safety population consists of subjects who received Palforzia or placebo in the controlled studies. This dataset includes a total of 709 subjects treated with Palforzia and 292 who received placebo in studies ARC003 and ARC007. The safety study ARC007 did not include a maintenance phase, requiring subjects only to attempt to up-dose to 300 mg Palforzia. Therefore, only data from the initial dose escalation and up-dosing phase in study ARC007 is included in the controlled safety population.

The integrated safety population consists of any subject who received at least one dose of Palforzia in both controlled and uncontrolled studies. No placebo data was included in the integrated safety population. This data set includes 812 subjects exposed to Palforzia in studies ARC003, ARC004, ARC007, and ARC011. Exposure to the maintenance dose of Palforzia varies in the integrated safety population because subjects continued the maintenance dose for up to 3 years in on-going studies. The cut-off date for submission of data to the original BLA from uncontrolled studies was July 15, 2018.

5.2 Demographics

Table 10 below shows the demographic characteristics of participants in both safety populations, with the controlled safety population stratified by treatment. The safety populations reflect the demographics of participants in study ARC003; more males than females participated in the studies, most participants were <17 years of age, and most of the participants were white and resided in North America. These demographic characteristics trends were noted in both Palforzia and placebo recipients with no major imbalances between the treatment groups identified.

Table 10: Demographic Characteristics of Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Integrated Population N (%)
Number of subjects	709	292	812
Gender:	--	--	--
Male	426 (60.1)	178 (61.0)	493 (60.7)
Female	283 (39.9)	114 (39.0)	319 (39.3)
Age (years):			

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Integrated Population N (%)
4 to 11	464 (65.4)	203 (69.5)	533 (65.6)
12 to 17	245 (34.6)	89 (30.5)	276 (34.0)
18 to 55[1]	0	0	3 (0.4)
Race	--	--	--
White	537 (75.7)	210 (71.9)	617 (76.0)
Black or African American	17 (2.4)	7 (2.4)	20 (2.5)
Asian	80 (11.3)	33 (11.3)	86 (10.6)
American Indian or Alaska Native	1 (0.1)	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	3 (0.4)	0	3 (0.4)
Multiple[2]	33 (4.7)	11 (3.8)	33 (4.1)
Other	38 (5.4)	30 (10.3)	52(6.4)
Ethnic origin	--	--	--
Hispanic or Latino	48 (6.8)	23 (7.9)	60 (7.4)
Not Hispanic or Latino	661 (93.2)	268 (91.8)	752 (92.6)
Geographic Region	--	--	--
North America	639 (90.1)	268 (91.8)	723 (89.0)
Europe	70 (9.9)	24 (8.2)	89 (11.0)
History of Asthma	--	--	--
Yes	373 (52.6)	142 (48.6)	418 (51.5)
No	336 (47.4)	150 (51.4)	394 (48.5)

Adapted from 125696/0: Summary of Clinical Safety, Table 7

[1] Includes subjects who turned 18 years of age prior to enrollment in ARC004

[2] Subjects in ARC007 were able to self-identify as multiracial and could select multiple categories

5.3 Overall Safety Profile

Table 13 below describes safety outcomes for both the controlled and integrated safety populations during each period (initial dose escalation, up-dosing, and maintenance) in study ARC003. All adverse events considered allergic reactions, except for systemic allergic reactions, were graded for severity using the CoFAR grading scale (Table 11). Individual symptoms comprising a systemic allergic reaction were graded individually using the CoFAR scale. The severity of systemic allergic reactions was graded using the European Academy of Allergy and Clinical Immunology (EAACI) (Table 12). The term anaphylaxis is used for systemic allergic reactions that are considered severe. The Common Terminology Criteria for Adverse Events (CTCAE) grading scale was used for coding the severity of all non-allergic adverse events.

Table 11: Consortium of Food Allergy Research (CoFAR) Criteria for Grading Allergic Reactions

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

Adapted from 125696/0 Summary of Clinical Safety

Table 12: Grading Criteria for Systemic Allergic Reactions and Anaphylaxis

Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**
-skin & subcutaneous tissues, GI, &/or mild respiratory - Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis	-mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms - Marked dysphagia, hoarseness and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness	- hypoxia, hypotension, or neurological compromise - Cyanosis or SpO_2 ≤ 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Adapted from 125696/0 Summary of Clinical Safety

Nominally more subjects in the controlled safety population who took Palforzia experienced any adverse event than placebo recipients (98.9% versus 94.9%). Overall, 89.1% of Palforzia recipients experienced adverse events related to the study product versus 57.5% of the placebo group. Adverse events decreased over time from up-dosing (97.5% and 91.3% of subjects Palforzia and placebo recipients, respectively) to the maintenance phase (87.1% and 79.7% in Palforzia and placebo recipients, respectively). Most adverse events were mild to moderate and decreased in severity from up-dosing to maintenance. Similarly, frequencies of adverse events related to allergic reactions and systemic allergic reactions decreased from the up-dosing phase to the maintenance phase. The reported events and trends in reactions in Palforzia-treated subjects in the controlled safety group were similar in the integrated safety population.

Subjects in the integrated safety population who took Palforzia for 0-13 weeks reported more adverse events (475/661 [71.9%]) compared to those who took the maintenance dose for 14-26

weeks (316/483 [65.4%]), 27-52 weeks (178/284 [62.7%]), and >52 weeks (95/178 [53.4%]). Allergic reactions also appeared to decrease over time (0-13 weeks (309/661 [46.7%]) compared to those who took the maintenance dose for 14-26 weeks (171/483 [35.4%]), 27-52 weeks (95/284 [33.5%]), and >52 weeks (39/178 [21.9%]).

Thirteen serious adverse events (SAEs) occurred in the safety population. In the controlled safety population (studies ARC003 and ARC007) SAEs were reported by 10/709 (1.4%) Palforzia recipients: 6 subjects (0.9%) during up-dosing and 4 subjects (1.3%) during maintenance, respectively. Three placebo recipients reported SAEs: 2 subjects (0.7%) during up-dosing and 1 subject (0.8%) during maintenance, respectively. Of these, 4 SAEs in Palforzia recipients were assessed as related to the study product: 3 anaphylactic reactions (2 during up-dosing, 1 during maintenance) and 1 asthma exacerbation during up-dosing. Two of 3 subjects who reported anaphylaxis SAEs discontinued from the study product. No SAEs in placebo recipients were considered related to the study product. The SAEs assessed as unrelated by the investigator in Palforzia recipients were mycoplasma pneumonia (1), asthma (1), gastroenteritis (1), streptococcal pharyngitis (1), concussion (1), and acute lymphocytic leukemia (1). In placebo recipients unrelated SAEs were appendicitis, humerus fracture, and craniocerebral injury. One death occurred in study ARC007. This subject, from the placebo group, suffered a fatal craniocerebral injury related to a motor vehicle accident.

In the integrated safety population, all of whom received at least one dose of Palforzia, (studies ARC003, ARC004, ARC007, and ARC011), 4 additional subjects experienced SAEs during maintenance in the follow-on studies. One systemic allergic reaction was considered related to the study product. This subject continued after a temporary dose interruption. The 3 unrelated SAEs were abdominal pain, dehydration, and streptococcal infection.

In addition to the overall adverse event profile, Table 13 provides a high-level summary of adverse events related to allergic reactions. These allergic reaction data are discussed in greater detail in Section 5.4: Adverse Events of Special Interest.

Table 13: Summary of Adverse Events by Dosing Period in Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Initial Dose Escalation:	--	--	--
Total Subjects in population	709	292	812
Subjects with one or more adverse event	376 (53.0)	93 (31.8)	419 (51.6)
Severity of adverse event:			
Mild	340 (48.0)	87 (29.8)	374 (46.1)
Moderate	36 (5.1)	6 (2.1)	44 (5.4)
Severe	0	0	1 (0.1)
Life-threatening	0	0	0
Adverse events leading to study product discontinuation	13 (1.8)	3 (1.0)	15 (1.8)
Adverse events related to study product	336 (47.4)	68 (23.3)	373 (45.9)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Subjects with at least one serious adverse event	0	0	0
Serious adverse events related to study product	0	0	0
Deaths[1]	0	0	0
Adverse events related to:	--	--	--
Anaphylaxis/Systemic allergic reaction	5 (0.7)	1 (0.3)	5 (0.6)
Allergic reaction[2]	344 (48.5)	76 (26.0)	382 (47.0)
Accidental food allergen exposure	1 (0.1)	2 (0.7)	2 (0.2)
Up-Dosing	--	--	--
Total Subjects in population	693	289	794
Subjects with one or more adverse event	676 (97.5)	264 (91.3)	769 (96.9)
Severity of adverse event			
Mild	319 (46.0)	178 (61.6)	364 (45.8)
Moderate	336 (48.5)	81 (28.0)	382 (48.1)
Severe	20 (2.9)	4 (1.4)	22 (2.8)
Life-threatening	1 (0.1)	0	1 (0.1)
Adverse events leading to study product discontinuation	67 (9.7)	4 (1.4)	73 (9.2)
Adverse events related to study product	599 (86.4)	143 (49.5)	678 (85.4)
Subjects with at least one serious adverse event	6 (0.9)	2 (0.7)	6 (0.8)
Serious adverse events related to study product	3 (0.4)	0	3 (0.4)
Deaths[1]	0	1	0
Adverse events related to:			
Anaphylaxis/Systemic allergic reaction	63 (9.1)	10 (3.5)	71 (8.9)
Allergic reaction[2]	589 (85.0)	181 (62.6)	668 (84.1)
Accidental food allergen exposure	80 (11.5)	55 (19.0)	95 (12.0)
Maintenance	--	--	--
Total Subjects in population	310	118	661
Subjects with one or more adverse event	270 (87.1)	94 (79.7)	541 (81.8)
Severity of adverse event			
Mild	161 (51.9)	57 (48.3)	344 (52.0)
Moderate	101 (32.6)	37 (31.4)	183 (27.7)
Severe	8 (2.6)	0	14 (2.1)
Life-threatening	0	0	0
Adverse events leading to study product discontinuation	4 (1.3)	0	7 (1.1)
Adverse events related to study product	159 (51.3)	26 (22.0)	352 (53.3)
Subjects with at least one serious adverse event	4 (1.3)	1 (0.8)	8 (1.2)
Serious adverse events related to study product	1 (0.3)	0	2 (0.3)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Deaths[1]	0	0	0
Adverse events related to:			
Anaphylaxis/Systemic allergic reaction	27 (8.7)	2 (1.7)	57 (8.6)
Allergic reaction[2]	169 (54.5)	48 (40.7)	386 (58.4)
Accidental food allergen exposure	28 (9.0)	24 (20.3)	56 (8.5)

Adapted from 125696/0: Summary of Clinical Safety, Table 10, Table 11, Table 14.3.1.1.1, and Table 14.3.1.1.2
[1] One death occurred in study ARC007. This subject, from the placebo group, suffered a fatal injury related to a motor vehicle accident.
[2] Allergic reactions also include systemic allergic reactions. Allergic reactions are defined by Consortium of Food Allergy Research (CoFAR) Criteria for Grading Allergic Reactions (Table 11)

Common Adverse Events:

Below are tables summarizing common adverse events by MedDRA preferred term for the controlled and integrated safety populations during up-dosing and maintenance periods. Adverse events were less frequent during the initial dose escalation which occurred over a 2-day period; however, similar common AEs were reported during initial dose escalation as those reported in the up-dosing and maintenance periods (data not shown).

The most common adverse events in the controlled safety population that were at least 5% higher in Palforzia recipients compared to placebo recipients were abdominal pain, throat irritation, pruritus, vomiting, cough, nausea, urticaria, upper abdominal pain, abdominal discomfort, oral pruritus, and sneezing. The frequency of these events decreased in the maintenance phase compared to the up-dosing phase. The frequency of these events was similar in the integrated safety population compared to Palforzia recipients in the controlled safety population throughout the 3 study periods.

Table 14: Summary of Common Adverse Events by Preferred Term Reported by at Least 5% of Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Up-Dosing:	--	--	--
Total Subjects in population	693	289	812
Subjects with at least 1 adverse event	676 (97.5)	264 (91.3)	769 (96.9)
Abdominal pain	314 (45.3)	51 (17.6)	346 (43.6)
Throat irritation	279 (40.3)	49 (17.0)	303 (38.2)
Pruritus	225 (32.5)	59 (20.4)	240 (30.2)
Vomiting	253 (36.5)	47 (16.3)	282 (35.5)
Cough	221 (31.9)	68 (23.5)	259 (32.6)
Nausea	224 (32.3)	41 (14.2)	249 (31.4)
Urticaria	197 (28.4)	54 (18.7)	222 (28.0)
Upper abdominal pain	209 (30.2)	39 (13.5)	237 (29.8)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Abdominal discomfort	172 (24.8)	35 (12.1)	189 (23.8)
Oral pruritus	174 (25.1)	19 (6.6)	191 (24.1)
Sneezing	140 (20.2)	31 (10.7)	154 (19.4)
Throat tightness	98 (14.1)	8 (2.8)	109 (13.7)
Oral paresthesia	94 (13.6)	11 (3.8)	100 (12.6)
Wheezing	85 (12.3)	21 (7.3)	95 (12.0)
Anaphylactic reaction	63 (9.1)	10 (3.5)	71 (8.9)
Tongue pruritus	63 (9.1)	10 (3.5)	71 (8.9)
Lip pruritus	62 (8.9)	6 (2.1)	69 (8.7)
Dyspnea	53 (7.6)	5 (1.7)	62 (7.8)
Ear pruritus	41 (5.9)	2 (0.7)	42 (5.3)
Chest discomfort	37 (5.3)	2 (0.7)	41 (5.2)
Maintenance	--	--	--
Total Subjects in population	310	118	661
Subjects with at least 1 adverse event	270 (87.1)	94 (79.7)	541 (81.8)
Abdominal pain	46 (14.8)	7 (5.9)	92 (13.9)
Throat irritation	43 (13.9)	11 (9.3)	105 (15.9)
Pruritus	45 (14.5)	14 (11.9)	90 (13.6)
Vomiting	50 (16.1)	14 (11.9)	107 (16.2)
Cough	61 (19.7)	22 (18.6)	129 (19.5)
Nausea	45 (14.5)	8 (6.8)	89 (13.5)
Urticaria	63 (20.3)	17 (14.4)	128 (19.4)
Upper abdominal pain	41 (13.2)	9 (7.6)	70 (10.6)
Abdominal discomfort	19 (6.1)	7 (5.9)	68 (10.3)
Oral pruritus	39 (12.6)	5 (4.2)	60 (9.1)
Sneezing	33 (10.6)	5 (4.2)	51 (7.7)
Throat tightness	20 (6.5%)	0	31 (4.7)
Oral paresthesia	23 (7.4)	2 (1.7)	33 (5.0)
Wheezing	19 (6.1)	10 (8.5)	39 (5.9)
Anaphylactic reaction	27 (8.7)	2 (1.7)	57 (8.6)
Tongue pruritus	10 (3.2)	1 (0.8)	24 (3.6)
Lip pruritus	12 (3.9)	1 (0.8)	30 (4.5)
Dyspnea	17 (5.5)	1 (0.8)	38 (5.7)
Ear pruritus	7 (2.3)	0	12 (1.8)
Chest discomfort	8 (2.6)	0	17 (2.6)

Adapted from 125696/0 Summary of Clinical Safety Table 14, Table 15, Table 14.3.1.2.1

Discontinuations due to Adverse Events:

In the controlled safety population, 1.8% of subjects Palforzia recipients and 1.0% of placebo recipients discontinued the study product during initial dose escalation. During up-dosing 9.7% in the Palforzia group and 1.4% in the placebo group discontinued during up-dosing. During maintenance, 1.3% of Palforzia recipients and none of placebo recipients discontinued the study product. The most common adverse events leading to discontinuation of the study product during initial dose escalation and up-dosing were gastrointestinal (GI) disorders including abdominal pain (3.5% Palforzia, 0.3% placebo), vomiting (2.7%, 0%), nausea (1.8%, 0%), and systemic allergic reaction, including anaphylaxis (1.6%, 0%). During maintenance, the most common reason was systemic allergic reaction in 0.6% of Palforzia recipients (0% placebo).

In the integrated safety population, the distribution was similar, as 1.8% of subjects discontinued during initial dose escalation, 9.2% during up-dosing, 1.1% during maintenance, and 11.6% overall. The most common adverse events leading to discontinuation were abdominal pain (3.7%), vomiting (2.5%), nausea (1.7%), systemic allergic reaction/anaphylaxis (1.7%).

Adverse events leading to discontinuation are summarized in the table below.

Table 15: Summary of Adverse Events by Preferred Term Leading to Discontinuation of Study Product in ≥2 Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Up-Dosing:	--	--	--
Total Subjects in population	693	289	794
Subjects with at least 1 adverse event	67 (9.7)	4 (1.4)	73 (9.2)
Abdominal pain	18 (2.6)	0	21 (2.6)
Vomiting	17 (2.5)	0	18 (2.3)
Nausea	10 (1.4)	0	11 (1.4)
Abdominal discomfort	6 (0.9)	0	6 (0.8)
Upper abdominal pain	6 (0.9)	0	6 (0.8)
Oral pruritus	3 (0.4)	0	3 (0.4)
Eosinophilic esophagitis	3 (0.4)	0	4 (0.5)
Gastroesophageal reflux disease	3 (0.4)	0	3 (0.4)
Retching	3 (0.4)	0	3 (0.4)
Salivary hypersecretion	2 (0.3)	0	2 (0.3)
Throat irritation	5 (0.7)	0	6 (0.8)
Throat tightness	3 (0.4)	1 (0.3)	3 (0.4)
Wheezing	3 (0.4)	1 (0.3)	3 (0.4)
Cough	3 (0.4)	0	3 (0.4)
Rhinorrhea	2 (0.3)	0	2 (0.3)
Systemic allergic reaction/anaphylaxis	9 (1.3)	0	9 (1.1)
Urticaria	5 (0.7)	0	5 (0.6)
Pruritus	2 (0.3)	0	2 (0.3)
Rash	2 (0.3)	0	2 (0.3)
Chest pain	2 (0.3)	0	2 (0.3)
Maintenance	--	--	--
Total Subjects in population	310	118	661
Subjects with at least 1 adverse event	4 (1.3)	0	7 (1.1)
Abdominal pain	0	0	0
Vomiting	0	0	0
Nausea	0	0	0
Abdominal discomfort	0	0	0
Upper abdominal pain	0	0	0
Oral pruritus	0	0	0
Eosinophilic esophagitis	0	0	0
Gastroesophageal reflux	0	0	0
Retching	0	0	0
Salivary hypersecretion	0	0	0
Throat irritation	0	0	1 (0.2)
Throat tightness	1 (0.3)	0	0
Wheezing	1 (0.3)	0	1 (0.2)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Cough	0	0	0
Rhinorrhea	0	0	0
Systemic allergic reaction/anaphylaxis	2 (0.6)	0	3 (0.5)
Urticaria	0	0	1 (0.2)
Pruritus	0	0	0
Rash	0	0	0
Chest pain	0	0	0

Adapted from 125696/0 Summary of Clinical Safety Table 28, Table, 29, and Table 14.3.1.10.1

5.4 Adverse Events of Special Interest

Select adverse events of special interest (AESIs) specific to oral immunotherapy as a treatment for IgE-mediated food allergy were identified through literature review of published studies. These events included systemic allergic reactions and anaphylaxis, use of epinephrine to treat allergic reactions, and eosinophilic esophagitis. A summary and discussion of the AESIs occurring in this study program are presented below.

Systemic Allergic Reactions and Anaphylaxis:

In the controlled population, 9.4% of subjects taking Palforzia reported systemic allergic reactions during initial dose escalation and up-dosing combined while 3.8% of subjects in the placebo group did. Most subjects who reported systemic allergic reactions reported only one episode. During initial dose escalation and up-dosing, 1.6% of Palforzia recipients discontinued due to systemic allergic reactions versus no placebo recipients. During maintenance, 8.7% Palforzia recipients and 1.7% placebo recipients reported systemic allergic reactions; 0.6% of Palforzia recipients and placebo recipients discontinued due to systemic allergic reaction. Three Palforzia recipients had a serious systemic allergic reaction, including 2 (0.3%) during up-dosing and 1 (0.3%) during maintenance treatment with Palforzia. During initial dose escalation and up-dosing combined, 6.1% of Palforzia recipients and 3.1% of placebo recipients had a systemic allergic reaction that required epinephrine use. Most of the epinephrine doses were administered outside of clinical facilities.

Between the two controlled studies, ARC003 and ARC007 (which did not require a DBPCFC for study randomization and therefore may have enrolled subjects less sensitive to small amounts of peanut protein), systemic allergic reactions and peanut allergy history were similar. In study ARC003 72.1% of participants reported a history of 1 or more systemic allergic reactions to peanut while in study ARC007 60% of participants reported a history of 1 or more systemic allergic reactions to peanut though most (85.7%) reported using epinephrine, antihistamines, or other medications to treat a qualifying[2] allergic reaction to peanut. In ARC003, 14.2% of Palforzia recipients reported systemic allergic reactions vs. 3% of placebo recipients. During study ARC007 10.7% of Palforzia recipients vs. 5.4% of placebo recipients reported a systemic allergic reaction. The differences in these reports are small; no conclusion can be made when

[2] Participants in ARC007 were eligible if the following criteria were met: history of physician-diagnosed IgE-mediated peanut allergy that includes the onset of characteristic allergic signs and symptoms within two hours of known oral exposure to peanut or a peanut-containing food, mean peanut wheal diameter on skin prick testing (SPT) of ≥ 8 mm greater than the negative saline control at screening, and serum IgE to peanut of ≥ 14 kUA/L at Screening.

comparing systemic allergic reactions across the two controlled studies, though overall, Palforzia treated subjects report more systemic reactions than placebo recipients.

Occurrence of systemic allergic reactions related to subject-reported accidental food exposures decreased from up-dosing (9 events in Palforzia recipients and 9 events in placebo recipients) to maintenance (3 events in Palforzia recipients and 1 event in placebo recipients). Similarly, occurrence of all adverse events related to subject-reported accidental food allergen exposures decreased from 11.5% of subjects during up-dosing to 9.0% during maintenance in Palforzia recipients. In placebo recipients, occurrence of these adverse events did not change from up-dosing (19.0%) to maintenance (20.3%). During maintenance dosing, 3.5% of accidental food exposures in Palforzia recipients versus 5.1% placebo recipients were reported to be related to peanut exposure (data not shown). As outlined in Table 16, none of these accidental exposures were due to unknown food allergens, however, subjects may not have been able to identify peanut as a clear trigger in some cases due food contamination with small amounts of peanut protein. While not formally explored in the efficacy analysis, these rates of allergic reactions related to subject-reported accidental food exposure support the efficacy findings demonstrating a Palforzia-related treatment benefit. In fact, these data may be more predictive than DBPCFC results of the real-world impact of Palforzia in preventing reactions due to accidental peanut exposure.

An analysis of the most common (at least 10% of subjects in either group) extrinsic co-factors that may have contributed to systemic allergic reactions in the pediatric controlled safety population are as follows: Exercise (40.4% Palforzia, 7.7% placebo), exposure to hot water (13.5%, 0%), intercurrent illness (12.4%, 0%), fasting (11.2%, 0%), and other (14.6%, 7.7%). Two (2.2%) Palforzia-treated subjects reported uncontrolled asthma, 5 (5.6%) Palforzia-treated subjects reported menstruation as a co-factor, and 3 (3.4%) Palforzia-treated subjects reported NSAID use a co-factor. No placebo subjects reported intercurrent illness or NSAID use as a co-factor while one reported menstruation. Among the 5 Palforzia recipients who reported anaphylaxis (a severe systemic allergic reaction), co-factors included exercise (3 subjects), exercise and fasting (1), or no cofactors (1). Three subjects reported serious systemic allergic reactions. Co-factors influencing these episodes were intercurrent illness (2) and no co-factors (1).

A similar proportion of subjects reported systemic allergic reactions in the integrated safety population. Occurrence of systemic allergic reactions decreased over time when evaluating subjects on the maintenance dosing schedule. Six systemic allergic reactions were reported in subjects who took a maintenance dose of Palforzia >52 weeks compared with 20 episodes at 27-52 weeks, 21 episodes at 14-26 weeks, and 32 episodes at 0-13 weeks.

Table 16: Summary of Systemic Allergic and Anaphylactic Reactions in Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Initial Dose Escalation[1]:	--	--	--
Total subjects in population	709	292	812

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Number of systemic allergic reactions[2]	5	1	5
Number of systemic allergic reactions by trigger	--	--	--
Study product	5	0	5
Food allergen	0	1	0
Non-food allergen	0	0	0
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	5 (0.7)	1 (0.3)	5 (0.6)
2 episodes	0	0	0
≥ 3 episodes	0	0	0
Severity of systemic allergic reaction[3]	--	--	--
Mild	5 (0.7)	1 (0.3)	5 (0.6)
Moderate	0	0	0
Severe (anaphylaxis)	0	0	0
Considered serious adverse event	0	0	0
Used epinephrine to treat reaction	3 (0.4)	1 (0.3)	3 (0.4)
Location of reaction	--	--	--
Other than study site[2]	0	1(0.3)	0
Study site	3 (0.4)	0	3 (0.4)
Up-Dosing:	--	--	--
Total subjects in population	693	289	794
Number of systemic allergic reactions[2]	76	10	85
Number of systemic allergic reactions by trigger	--	--	--
Study product	63	1	68
Food allergen	8	9	12
Non-food allergen	5	0	5
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	50 (7.2)	10 (3.5)	57 (7.2)
2 episodes	13 (1.9)	0	14 (1.8)
≥ 3 episodes	0	0	0
Severity of systemic allergic reactions[3]			
Mild	24 (3.5)	4 (1.4)	28 (3.5)
Moderate	35 (5.1)	6 (2.1)	38 (4.8)
Severe (anaphylaxis)	4 (0.6)	0	5 (0.6)
Considered serious adverse event	2 (0.3)	0	2 (0.3)
Used epinephrine to treat reaction	41 (5.9)	8 (2.8)	47 (5.9)
Location of reaction			
Home	33 (4.8)	7 (2.4)	38 (4.8)
Study site	11 (1.6)	1 (0.3)	13 (1.6)
Maintenance	--	--	--
Total subjects in population	310	118	661
Number of systemic allergic reactions[2]	33	2	79
Number of systemic allergic reactions by trigger	--	--	--
Study product	28	1	66
Food allergen	4	1	11

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Non-food allergen	1	0	2
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	23 (7.4)	2 (1.7)	46 (70)
2 episodes	2 (0.6)	0	3 (0.5)
≥ 3 episodes	2 (0.6)	0	7 (1.1)
Severity of systemic allergic reactions[3]	--	--	--
Mild	12 (3.9)	0	25 (3.8)
Moderate	14 (4.5)	2 (1.7)	26 (3.9)
Severe (anaphylaxis)	1 (0.3)	0	5 (0.8)
Considered serious adverse event	1 (0.3)	0	2 (0.3)
Used epinephrine to treat reaction	19 (6.1)	2 (1.7)	43 (6.5)
Location of reaction	--	--	--
Other than study site	18 (5.8)	1 (0.8)	40 (6.1)
Study site	2 (0.6)	1 (0.8)	4 (0.6)

Adapted from 125696/0 Summary of Clinical Safety Table 31, Table 33, Table 14.3.7.4.1, Table 14.3.7.4.2
N = number of subjects
[1] Administration of study product was done entirely in clinic during the initial dose escalation period
[2]Number of systemic reactions occurring during the studies. This number does not denote the number of subjects in which systemic reactions occurred
[3] Anaphylaxis graded by severity by European Academy of Allergy and Clinical Immunology (EAACI) grading scale (Table 12)

Use of Epinephrine:

In the controlled safety population 10.4% of subjects in Palforzia recipients and 4.8% of placebo recipients had at least 1 episode of epinephrine use during initial dose escalation and up-dosing combined. During maintenance 7.7% of subjects Palforzia recipients 3.4% of placebo recipients had at least 1 episode of epinephrine use. An episode was defined as the administration of 1 or more epinephrine doses within 2 hours. During initial dose escalation and up-dosing combined epinephrine use to treat systemic allergic reactions was reported by 6.1% of Palforzia recipients and 3.1% of placebo recipients. During maintenance 6.1% of Palforzia recipients versus 1.7% of placebo recipients used epinephrine to treat systemic allergic reactions. All of the reactions requiring epinephrine during the initial dose escalation occurred at the study site. Approximately 70% of the reactions occurred at home during the up-dosing period, while approximately 90% occurred at home during the maintenance period. This breakdown is expected given the Palforzia dosing procedures. It is notable that the imbalance between Palforzia and placebo treated subjects is maintained regardless of the location of the reaction (study site vs. home).

In the integrated safety population, 2.0% of subjects reported at least 1 episode of epinephrine use during initial dose escalation, 9.9% during up-dosing and 8.2% during maintenance. Most epinephrine use in the integrated safety population was used to treat systemic allergic reactions.

Table 17: Summary of Use of Epinephrine as Rescue Medication in Subjects 4 through 17 Years of Age: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Initial Dose Escalation:	--	--	--
Total subjects in population	709	292	812
Subjects with any use of epinephrine	12 (1.7)	2 (0.7)	16 (2.0)
Age subcategory	--	--	--
4-11 years	7 (58.3)	2 (100.0)	10 (62.5)
12- <18 years	5 (41.7)	0	6 (37.5)
Number of epinephrine doses per episode			
1 dose	12 (100.0)	2 (100.0)	15 (93.8)
2 doses	0	0	1 (6.3)
≥3 doses	0	0	0
Severity of AE associated with the episode	--	--	--
Grade 1	8 (66.7)	1 (50.0)	9 (56.3)
Grade 2	4 (33.3)	1 (50.0)	6 (37.5)
Grade 3	0	0	1 (6.3)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	0	1 (50.0)	0
Study site	12 (100.0)	1 (50.0)	16 (100.0)
Up-Dosing:	--	--	--
Total subjects in population	693	289	794
Subjects with any use of epinephrine	67 (9.7)	12 (4.2)	79 (9.9)
Age subcategory	--	--	--
4-11 years	35 (52.2)	8 (66.7)	40 (50.6)
12- <18 years	32 (47.8)	4 (33.3)	39 (49.4)
Number of epinephrine doses per episode	--	--	--
1 dose	72 (87.8)	11 (91.7)	86 (88.7)
2 doses	9 (11.0)	1 (8.3)	10 (10.3)
≥3 doses	1 (1.2)	0	1 (1.01)
Severity of AE associated with the episode[1]	--	--	--
Grade 1	29 (35.4)	5 (41.7)	33 (34.0)
Grade 2	44 (53.7)	7 (58.3)	53 (54.6)
Grade 3	7 (8.5)	0	8 (8.2)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	58 (70.7)	11 (91.7)	67 (69.1)
Study site	24 (29.3)	1 (8.3)	30 (30.9)
Maintenance	--	--	--
Total subjects in population	310	118	661

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Total Palforzia Recipients in Integrated Population N (%)
Subjects with any use of epinephrine	24 (7.7)	4 (3.4)	54 (8.2)
Age sub category	--	--	--
4-11 years	10 (41.7)	4 (100)	29 (53.7)
12-17 years	14 (58.3)	0	25 (46.3)
Number of epinephrine doses per episode	--	--	--
1 dose	27 (93.1)	4 (100.0)	70 (95.9)
2 doses	1 (3.4)	0	2 (2.7)
≥3 doses	1 (3.4)	0	1 (1.4)
Severity of AE associated with the episode	--	--	--
Grade 1	12 (41.4)	2 (50.0)	26 (35.6)
Grade 2	16 (55.2)	2 (50.0)	43 (58.9)
Grade 3	1 (3.4)	0	4 (5.5)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	26 (89.7)	3 (75.0)	67 (91.8)
Study site	3 (10.3)	1 (25.0)	6 (8.2)

Adapted from 125696/0 Clinical Summary of Safety Table 34, Table 35, and Table 14.3.7.3.1
N = number of subjects
[1] Grading criteria is missing for 2 episodes occurring during up-dosing in the controlled safety population and for 3 episodes during up-dosing in the integrated safety population. See Table 12 and 13 for grading criteria.

Eosinophilic Esophagitis:

In the controlled safety population, 3/693 (0.4%) Palforzia recipients developed biopsy confirmed eosinophilic esophagitis (EoE) during up-dosing. In the integrated safety population, 1 additional subject was diagnosed with EoE during up-dosing. Three of these episodes were considered on-going at the time of BLA submission. Another subject diagnosed with biopsy confirmed EoE in study ARC004 was reported in a safety update submitted to the BLA for on-going studies. This episode was considered on-going. The frequency of EoE in subjects taking Palforzia is 0.6% (5/812) in the pediatric integrated safety population. One subject in ARC001 was diagnosed with biopsy confirmed EoE one month after withdrawing from the study during the up-dosing phase at the 12mg dose due to vomiting (this case was considered on-going), one subject in ARC002 (a former placebo subject from ARC001) developed biopsy confirmed EoE during Palforzia treatment (considered on-going), and one adult subject in ARC004 also developed biopsy confirmed EoE during maintenance dosing (this case was considered resolved). In addition, 4 reports of biopsy-confirmed EoE (all considered on-going) in Palforzia recipients occurred in ARC008. Overall 12 subjects in the clinical program have developed EoE. No subjects taking placebo were diagnosed with EoE in this clinical development program.

5.5 Safety in Asthmatics

Subjects with uncontrolled or severe asthma were specifically excluded from study participation; however, asthma was a common co-morbidity with approximately half of the controlled study population reporting an asthma diagnosis. Overall, adverse events occurred at a similar frequency in Palforzia recipients regardless of asthma history. Respiratory-specific

adverse events occurred more frequently in subjects with a history of asthma compared to those without asthma (Table 18 below). These events include asthma, wheezing, dyspnea and throat tightness. Palforzia-treated subjects with asthma reported increased incidence of dyspnea and throat tightness than subjects with asthma in the placebo group.

In the controlled safety population, among subjects with a history of asthma, systemic allergic reactions occurred more frequently in those taking Palforzia compared to placebo recipients (9.7% during up-dosing and 7.7% during maintenance in Palforzia recipients vs. 3.5% up-dosing and 1.6% maintenance in placebo recipients). In subjects with no history of asthma, Palforzia recipients reported more systemic allergic reactions (8.4% up-dosing and 9.7% maintenance) compared to placebo recipients (3.4% up-dosing and 1.8% maintenance). Further analysis shows subjects with a history of asthma taking Palforzia reported more moderate systemic allergic reactions (but not more mild or severe reactions) during up-dosing compared to subjects without asthma (6.1% vs 3.9%). Similar rates of mild, moderate, and severe systemic reactions occurred during maintenance in both subpopulations (data not shown). Epinephrine use was reported more frequently in asthmatic subjects taking Palforzia during up-dosing compared to those with no history of asthma (10.5% vs. 8.7%). During maintenance, this percentage was similar in asthmatics compared to non-asthmatics taking Palforzia (7.7% vs. 7.8%).

The overall AE profile was similar in subjects with an asthma history regardless of treatment assignment; however, a clinical history of asthma may increase the number of moderate systemic allergic reactions and epinephrine use in those taking Palforzia during the up-dosing period. In addition, the Asthma Control Test (ACT) was administered for studies ARC003, ARC007, ARC004, and ARC011 at baseline and throughout the studies. No concerning change in subjects' asthma control was noted in subjects 4 to 11 years of age or 12 to 17 years of age (data not shown), suggesting that although subjects with asthma reported increased occurrence of some respiratory-related adverse events, these events did not affect overall asthma control.

Table 18: Summary of Respiratory Adverse Events by Preferred Term in Subjects 4 through 17 Years of Age With and Without Asthma: Controlled Safety Population

	Palforzia Recipients With Asthma N (%)	Placebo Recipients With Asthma N (%)	Palforzia Recipients Without Asthma N (%)	Placebo Recipients Without Asthma N (%)
Up-Dosing:	--	--	--	--
Total Subjects in population	361	141	332	148
Asthma	41 (11.4)	15 (10.6)	3 (0.9)	1 (0.7)
Cough	117 (32.4)	34 (24.1)	104 (31.3)	34 (23.0)
Wheezing	55 (15.2)	15 (10.6)	30 (9.0)	6 (4.1)
Dyspnea	40 (11.1)	4 (2.8)	13 (3.9)	1 (0.7)
Dysphonia	10 (2.8)	2 (1.4)	16 (4.8)	1 (0.7)
Chronic throat clearing	8 (2.2)	1 (0.7)	6 (1.8)	1 (0.7)
Throat irritation	147 (40.7)	22 (15.6)	132 (39.8)	27 (18.2)
Throat tightness	65 (18.0)	6 (4.3)	33 (9.9)	2 (1.4)
Upper-airway cough syndrome	9 (2.5)	1 (0.7)	3 (0.9)	0
Exercise-induced asthma	2 (0.6)	1 (0.7)	0	0
Maintenance	--	--	--	--

Total Subjects in population	156	61	154	57
Asthma	19 (12.2)	6 (9.8)	1 (0.6)	1 (1.8)
Cough	30 (19.2)	11 (18.0)	31 (20.1)	11 (19.3)
Wheezing	13 (8.3)	6 (9.8)	6 (3.9)	4 (7.0)
Dyspnea	12 (7.7)	1 (1.6)	5 (3.2)	0
Dysphonia	5 (3.2)	1 (1.6)	3 (1.9)	0
Chronic throat clearing	1 (0.6)	1 (1.6)	0	1 (1.8)
Throat irritation	21 (13.5)	5 (8.2)	22 (14.3)	6 (10.5)
Throat tightness	10 (6.4)	0	10 (6.5)	0
Upper-airway cough syndrome	0	0	2 (1.3)	0
Exercise-induced asthma	0	0	0	0

Adapted from 125696/0 Clinical Summary of Safety Table 14.3.1.2.27 and Table 14.3.1.2.29
N = number of subjects

5.6 Safety in Adults

The safety data for adult participants in the Palforzia clinical program is presented for completeness. A small number of adults 18 to 55 years of age participated in the Phase 3 studies, ARC003 and ARC004. This section summarizes selected data in the adult population with special attention to AESIs. Demographic data for adults participating in ARC003 can be found in Table 3, Section 4.2. Adult subject disposition can be found in Table 4, Section 4.2.

In study ARC003 55 adults participated (41 received Palforzia, 14 received placebo). Of this group, 24 subjects (16 formerly treated with Palforzia and 8 from the placebo group) were enrolled in ARC004 to take Palforzia for an additional 3 years to evaluate the safety of long-term maintenance immunotherapy.

In study ARC003, adult subjects reported similar rates of adverse reactions compared to the pediatric population. Overall, 41 (100%) of Palforzia recipients experienced AEs compared to 13 (92.9%) subjects in the placebo group. The majority of AEs in the Palforzia group were mild (29.3%) to moderate (65.9%). In the placebo group, the majority of AEs were also mild (35.7%) to moderate (50%). See Table 19 below for a more detailed summary of AEs in adult subjects.

Table 19: Summary of Adverse Events by Dosing Period in the Adult Safety Population 18 to 55 Years of Age: Study ARC003

	Palforzia N (%)	**Placebo N (%)**
Initial Dose Escalation:	--	--
Total Subjects in population	41	14
Subjects with one or more adverse event	20 (48.8)	2 (14.3)
Severity of adverse event:		
Mild	19 (46.3)	2 (14.3)
Moderate	1 (2.4)	0
Severe	0	0
Adverse events leading to study product discontinuation	1 (2.4)	0
Adverse events related to study product	20 (48.8)	2 (14.3)
Subjects with at least one serious adverse event	0	0
Serious adverse events related to study product	0	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	0	0

	Palforzia N (%)	Placebo N (%)
Allergic reaction	18 (43.9)	2 (14.3)
Accidental food allergen exposure	0	0
Up-Dosing	--	--
Total Subjects in population	39	14
Subjects with one or more adverse event	38 (97.4)	13 (92.9)
Severity of adverse event		
Mild	14 (35.9)	7 (50.0)
Moderate	23 (59.0)	6 (42.9)
Severe	1 (2.6)	0
Adverse events leading to study product discontinuation	5 (12.8)	0
Adverse events related to study product	35 (89.7)	8 (57.1)
Subjects with at least one serious adverse event	0	0
Serious adverse events related to study product	0	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	4 (10.3)	0
Allergic reaction	33 (84.6)	10 (71.4)
Accidental food allergen exposure	5 (12.8)	2 (14.3)
Maintenance	--	--
Total Subjects in population	25	14
Subjects with one or more adverse event	22 (88.0)	8 (57.1)
Severity of adverse event		
Mild	8 (32.0)	4 (28.6)
Moderate	13 (52.0)	3 (21.4)
Severe	1 (4.0)	1 (7.1)
Adverse events leading to study product discontinuation	1 (4.0)	0
Adverse events related to study product	13 (52.0)	1 (7.1)
Subjects with at least one serious adverse event	2 (8.0)	1 (7.1)
Serious adverse events related to study product	1 (4.0)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	5 (20.0)	1 (7.1)
Allergic reaction	14 (56.0)	4 (28.6)
Accidental food allergen exposure	4 (16)	3 (21.4)
Overall	--	--
Total Subjects in population	41	14
Subjects with one or more adverse event	41 (100.0)	13 (92.9)
Severity of adverse event	--	--
Mild	12 (29.3)	5 (35.7)
Moderate	27 (65.9)	7 (50.0)
Severe	2 (4.9)	1 (7.1)
Adverse events leading to study product discontinuation	7 (17.1)	0 (0.0)
Adverse events related to study product	38 (92.7)	10 (71.4)
Subjects with at least one serious adverse event	2 (4.9)	1 (7.1)
Serious adverse events related to study product	1 (2.4)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	8 (19.5)	1 (7.1)
Allergic reaction	36 (87.8)	11 (78.6)

	Palforzia N (%)	Placebo N (%)
Accidental food allergen exposure	8 (19.5)	4 (28.6)

Adapted from 125696/0 Clinical Study Report ARC003 Table 14.3.1.15.4
N = number of subjects

Common adverse events in adults (study ARC003) also occurred at similar frequencies compared to pediatric subjects. The most common AEs occurring overall in Palforzia recipients compared to placebo recipients included abdominal pain (43.9% vs. 42.9%), vomiting (12.2% vs 21.4%), pruritus (39.0% vs. 14.3%), upper abdominal pain (39.0% vs. 28.6%), cough (29.3% vs. 21.4%), throat irritation (29.3% vs. 14.3%), oral pruritus (36.6% vs. 28.6%), nausea (48.8% vs. 21.4%) and urticaria (29.3% vs. 21.4%).

An increased percentage of adult subjects in the ARC003 Palforzia group had systemic allergic reactions compared to placebo: 8/41 (19.5%) vs. 1/14 (7.1%), respectively. Three subjects experienced systemic allergic reactions during up-dosing and 4 during maintenance. One subject had 2 reactions, 1 during up-dosing and 1 during maintenance. One subject in the placebo group had a moderate systemic allergic reaction due to an accidental food exposure and was not treated with epinephrine. No adult had a reaction considered anaphylaxis (a severe systemic allergic reaction). Epinephrine use in adult subjects followed a similar trend as observed in pediatric subjects with more subjects treated with Palforzia using epinephrine to treat allergic symptoms. Overall, 7/41 (17.1%) of subjects treated with Palforzia used epinephrine as a rescue medication while 1/14 (7.1%) in the placebo group did.

One adult developed EoE in study ARC004 during maintenance dosing.

6.0 Special Populations

Pediatric

The applicant seeks an indication for use of Palforzia in individuals 4 through 17 years of age. If Palforzia is approved in this age group, the applicant plans to conduct a study to characterize the safety and effectiveness of Palforzia in subjects 1 to < 4 years of age. The applicant has requested a partial waiver for subjects < 1 year of age as necessary studies are impossible or highly impracticable because peanut allergy is not typically diagnosed before the age of 1 year.

Elderly

No studies in the clinical development program included individuals > 65 years of age. The applicant does not seek an indication for use in this age group.

Pregnancy

In the clinical development program, pregnant subjects were excluded. Female subjects of childbearing potential were required to have a pregnancy test prior to enrollment and during study participation. No subject became pregnant in the clinical development program. There are no safety or effectiveness data to support initiation in pregnancy. In Section 8.1 of the Prescribing Information (PI), the applicant plans to state that treatment with Palforzia should not be initiated during pregnancy.

Immunocompromised individuals
The pre-licensure clinical studies that evaluated Palforzia excluded individuals on immunomodulatory medications. Therefore, no data are available on the safety or effectiveness of Palforzia in this population.

7.0 Summary and Focus of Questions to the Committee

The pre-specified efficacy success criterion for the Phase 3 study, ARC003, was met for subjects 4 through 17 years of age. The difference between Palforzia and placebo groups in proportion of subjects able to ingest 600 mg of peanut protein with no more than mild symptoms during the DBPCFC at study end was 63.2% with a 95% CI of (53.0%, 73.3%). While not evaluated as an efficacy outcome, adverse events related to subject-reported accidental food allergen exposures decreased from 11.5% during up-dosing to 9.0% during maintenance in the Palforzia treatment group, further suggesting that Palforzia protects against allergic reactions following accidental exposure. In the placebo group, the incidence of these events did not change from up-dosing (19.0%) to maintenance (20.3%).

Treatment with Palforzia resulted in an increased risk of systemic allergic reactions, some of which resulted in increased epinephrine use compared to the placebo treated group. In the controlled population, during initial dose escalation and up dosing combined, 9.4% of subjects taking Palforzia reported systemic allergic reactions while 3.8% of subjects in the placebo group did. During initial dose escalation and up-dosing combined, 6.1% of Palforzia recipients and 3.1% of placebo recipients had a systemic allergic reaction that required epinephrine use. During maintenance, 6.1% of Palforzia recipients used epinephrine to treat a systemic allergic reaction while 1.7% of placebo recipients did. A substantial proportion of subjects treated with Palforzia discontinued due to adverse events (9.0% of the pediatric population and 14.3% of adults in ARC003) with additional subjects withdrawing due to withdrawal of informed consent and other reasons. In addition, in the controlled safety population, 3 Palforzia treated subjects developed treatment-emergent biopsy confirmed EoE compared to no such cases in placebo recipients. Additional reports of EoE were seen in Palforzia treated subjects from follow-on studies.

The Committee will be asked whether the efficacy and safety data support licensure of Palforzia as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients 4 through 17 years of age with a confirmed diagnosis of peanut allergy.

8.0 References

1. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA. ICON: food allergy. J Allergy Clin Immunol. 2012 Apr;129(4):906-20.

2. Sampson HA et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014 Nov;134(5):1016-25.e43.

3. Adkinson, N. Franklin, Bruce S. Bochner, A. Wesley Burks, W. W. Busse, S. T. Holgate, Robert F. Lemanske, Robyn E. O'Hehir, and Elliott Middleton. Middleton's Allergy: Principles and Practice. 8th ed. 2014 Philadelphia: Elsevier/Saunders, PA. Print.

4. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014 Feb;133(2):291-307.

5. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS Data Brief. 2013 May;(121):1-8.

6. Lebovidge JS, Strauch H, Kalish LA, Schneider LC. Assessment of psychological distress among children and adolescents with food allergy. J Allergy Clin Immunol. 2009 Dec;124(6):1282-8.

7. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, Clarke A. Accidental ingestions in children with peanut allergy. J Allergy Clin Immunol. 2006 Aug;118(2):466-72.

8. Cherkaoui S, Ben-Shoshan M, Alizadehfar R, et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. Clin Transl Allergy. 2015;5:16.

9. Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. JAllergy Clin Immunol. 2011 Jul;128(1):110-115

10. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. 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. 2012;130(6):1260-74

11. Allan Bock, Anne Muñoz-Furlong, Hugh A. Sampson, Further fatalities caused by anaphylactic reactions to food, 2001-2006, Journal of Allergy and Clinical Immunology, Volume 119, Issue 4, April 2007, Pages 1016-1018

12. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233-43.