

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

Date: October 14, 2019

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Chair, BLA review committee
Office of Vaccines and Related Product Applications

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Subject: Original BLA submission Pharmacovigilance Review

Applicant: Aimmune Therapeutics, Inc.

Product: PALFORZIA
Peanut [*Arachis hypogaea*] Allergen Powder

AR 101 (product designation in clinical trials)

Proposed Indication: As treatment to reduce the risk of anaphylaxis after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.

STN: BLA 125696/0

Submission Date: December 21, 2018

Action Due Date: January 25, 2020

1. INTRODUCTION

a. Objectives

The purpose of this memorandum is to assess the adequacy of the sponsor's pharmacovigilance plan for AR101 (proposed trade name: PALFORZIA).

b. Background

Most food allergy begins during the first two years of life, and can manifest in a variety of chronic or recurrent conditions such as atopic dermatitis, contact urticaria, oral allergy syndrome and eosinophilic gastrointestinal disorders, as well as acute, life-threatening anaphylactic reactions[1] [2]. The clinical signs and symptoms of anaphylaxis include urticaria, respiratory compromise, gastrointestinal symptoms and hemodynamic and cardiovascular instability [3], which left untreated may result in death.

While many common food allergies resolve by late childhood or adolescence, peanut and tree nut allergies are more likely to remain active into adulthood[4]. Peanut allergy is the leading cause of fatal food-induced anaphylaxis in the US [5] and is estimated to affect slightly more than 1% of children in the US [5], with associated risks based upon both heritable and environmental factors. Concordance rates for peanut allergy are 64% for monozygotic twins and 7% for dizygotic twins [4], while the odds ratio for the risk of peanut allergy in subjects with a sibling with peanut allergy has been estimated between 6.7 to 13.5 [5, 6].

Factors associated with life-threatening allergic reactions to peanut include a history of anaphylaxis to peanut, comorbid conditions (e.g., asthma, cardiovascular disease, mastocytosis), concurrent use of certain medications (e.g., nonselective beta blockers and NSAIDs), and exercise, with teenagers and young adults at increased risk [6]. Risk-taking behavior in teenagers and young adults, such as failure to avoid triggers, failure to carry an epinephrine auto-injector, and alcohol use are thought to contribute to severe or fatal anaphylaxis [7]. The severity of chronic atopic disease such as asthma has been associated with the severity of peanut-induced acute allergic reactions [8]. Information on fatalities due to peanut allergy, largely from registries and retrospective reporting, indicates that concomitant asthma, lack of ready access to epinephrine, and consumption of foods outside the home are notable factors increasing the risk of death.[9-13]. Thus, the severity of an allergic reaction after accidental allergen exposure can be unpredictable.

Accidental peanut exposures are common; available literature notes that 55% of enrolled peanut allergic patients experienced at least one allergic reaction over a five-year period [14]), and emergency department visits are frequent (22.9% of peanut-allergic children in one year [15]).

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. Per the briefing document for the September 2019 FDA Allergenic Products Advisory Committee meeting, treatment is currently 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. If approved, PALFORZIA, will become the first approved treatment for a food allergy.

c. Product information

i. Product indication/description

Peanut [*Arachis hypogaea*] Allergen Powder (Trade Name PALFORZIA), also referred to as AR101, is proposed to be indicated as an oral immunotherapy treatment (OIT) to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. It is not intended for the immediate relief of allergic symptoms, and it is to be used in conjunction with a peanut-avoidant diet.

The product consists of characterized peanut allergen in the form of peanut flour with (b) (4) and packaged in graduated doses. Depending on dose level, AR101 contains the following inactive ingredients: microcrystalline cellulose, partially pregelatinized maize starch (0.5 mg, 1 mg, 10 mg, 20 mg capsule presentations only), magnesium stearate, colloidal silicon dioxide. The inactive ingredients are pharmaceutical grade. (b) (4)

AR101 is encapsulated in hydroxypropyl methyl cellulose (HPMC) capsules or filled in foil-laminate sachets. Doses are expressed as milligrams of peanut protein. The capsules do not contain animal-derived or sourced materials and meet global pharmaceutical standards. Five capsule dosage strengths of 0.5, 1, 10, 20, and 100 mg, and a single sachet dosage strength of 300 mg are available.

ii. Treatment regimen

Peanut-allergy treatment with AR101 has 3 phases, including initial dose escalation (IDE), up-dosing, and maintenance:

- IDE involves initiation of AR101 under medical supervision, using five single doses of 0.5, 1, 1.5, 3 and 6 mg of the product administered at 20-30-minute intervals as tolerated by the patient.
- Up-dosing (dose escalation) occurs every 2 weeks at 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. With the first dose of each escalation administered under medical supervision and the remaining doses taken by the patient at home.
- Maintenance dosing is 300 mg/day.

The capsules are not to be swallowed but rather opened and mixed with age-appropriate food. Similarly, the sachets are to be opened and mixed with age-appropriate food.

iii. Pertinent regulatory history

AR101 was granted Fast Track designation for peanut-sensitive adults and children on September 05, 2014.

Breakthrough Therapy designation was granted for peanut-sensitive children and adolescents aged 4 to 17 years on June 15, 2015.

AR101 has not been authorized in any country to date.

On September 13, 2019, the Allergenic Products Advisory Committee (APAC) meeting discussed the efficacy and safety data for Palforzia. The committee voted 7 to 2 that the efficacy data, and 8 to 1 that the safety data, in conjunction with a Risk Evaluation and Mitigation Strategy (REMS), are adequate to support the approval of PALFORZIA.

2. MATERIALS REVIEWED

a. STN 125696.0.0

- i. Module 1.16 Risk Management Plan
- ii. Module 1.14 Sponsor's proposed label
- iii. Module 2.7.4 Integrated Summary of Safety (ISS)
- iv. Module 5.3.5 Clinical Study Reports for ARC003, ARC007
- v. Module 5.3.5.3 ISS Updates of Anaphylaxis and Eosinophilic Esophagitis
- vi. FDA Briefing Document for Allergenic Products Advisory Committee meeting [September 13, 2019]

b. STN 125696.0.3

- i. Updated study protocols for ARC004, ARC008 and ARC011

c. STN 125696.0.7 Module 2.7.4 Updates

- i. Summary of Clinical Safety - update
- ii. Integrated Safety Summary Narratives: Full draft narratives for specified adverse events (anaphylaxis and eosinophilic esophagitis) from ongoing studies: ARC004, R008 and ARC011

3. CLINICAL SAFETY DATABASE

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) and three studies (ARC004, ARC008 and ARC011) are on-going. 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.

The **combined controlled safety database** includes 709 subjects, 4-17 years of age, treated with AR101, and 292 subjects treated with placebo in the completed, randomized, double-blind, placebo-controlled phase 3 studies, ARC003 and ARC007.

The **integrated safety database** 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. The integrated safety population includes 812 unique subjects, 4-17 years of age, who received at least 1 dose of AR101 study product, including the 709 subjects described above, with the remaining 103 subjects from the ongoing, uncontrolled, follow-on studies, ARC004 (ARC003 extension study) and ARC011 (ARC007 extension study).

Available safety data are summarized separately below for ARC008, an ongoing, open-label follow-on study. Subjects enrolled in ARC008 were subjects who had previously been enrolled in a different AR101 study; these subjects had either been in a placebo arm or had not been able to complete or tolerate the final phase of the treatment arm of the study in which they had been originally enrolled.

a. Trial Synopses

Synopses of trials providing safety data for this evaluation are in the table below:

Table 1: Listing of Clinical Studies (From STN 125696/0, Module 5.2 Listing of Clinical Studies, Module 2.7.4 Integrated Summary of Safety, Module 2.7.6 Synopses of Individual Studies)

ARC003 (NCT02635776, 2015-004257-41) Peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults (PALISADE)	
Study Design	Phase 3, international, RDBPC (NA)
Objectives	Efficacy, safety
Dosing Regimen	AR101 or placebo (3:1); IDE, up-dosing to 300 mg QD over 6 mos. (20-40 weeks); maintenance at 300 mg QD for 24-28 weeks
Median Treatment Duration ²	6 months (maximum 68 weeks)
Peanut Food Challenge	DBPCFC at exit
Number Enrolled/Treated	555 / 551
Status	Completed
ARC007 (NCT03126227) Real-world AR101 market-supporting experience study in peanut-allergic children ages 4-17 yrs. (RAMSES)	
Study Design	Phase 3, multicenter, RDBPC (NA)
Objectives	Safety

Dosing Regimen	AR101 or placebo (2:1); IDE, up-dosing to 300 mg QD over 6 mos. (20-40 weeks); NOTE: no maintenance phase
Median Treatment Duration ²	5.6 months
Peanut Food Challenge	No
Number Enrolled/Treated	506 / 505
Status	Completed
ARC004 (NCT02993107, 2016-004941-94) Peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults (PALISADE) follow-on study (nondaily maintenance)	
Study Design	Phase 3, international, OL follow-on for ARC003 (NA)
Objectives	Safety, efficacy
Dosing Regimen	Former placebo-treated: Up-dosing to 300 mg QD for 24 weeks, All: 300 mg QD, QOD, BIW, QW, or QOW
Median Treatment Duration ²	Up to 3 years
Peanut Food Challenge	Former placebo-treated: DBPCFC after 300 mg QD x 24 weeks; All: DBPCFC at exit
Number Enrolled/Treated	388 / 380 ³
Status	Ongoing
ARC011 (NCT03337542) Real-world experience, open-label extension study (RAMSES OLE)	
Study Design	Phase 3, multicenter, open-label maintenance for ARC007 (AR101-treated) (NA)
Objectives	Safety
Dosing Regimen	AR101 300 mg QD
Treatment Duration	~6 months
Peanut Food Challenge	No
Number Enrolled/Treated	237 / 226 ³
Status	Ongoing
ARC008 (NCT03292484, 2017-001334-26) A multicenter, open-label, long-term safety study of AR101 characterized oral desensitization immunotherapy in subjects who participated in a prior AR101 study	
Study Design	Phase 3, international, OL, long-term (3 years) follow-on for current / future AR101 studies (NA, EU)
Objectives	Safety, efficacy
Dosing Regimen	Tolerated daily or non-daily AR101 in originating study: 300 mg QD, QOD, BIW, QW, or QOW
	Received placebo or did not complete dosing or tolerate nondaily AR101 in originating study: Repeat or start up-dosing to 300 mg QD
Peanut Food Challenge	Optional OLFC/RWPC every 12 months (if ≥18 months x 300 mg QD)
Treatment Duration	Up to 3 years
Number Enrolled/Treated	360 / 339 ³
Status	Ongoing

1: Protocol number (ClinicalTrials.gov, EudraCT) as applicable.

2: Duration of treatment for the primary study population (4-26 years for ARC001, ARC002, and 4-17 years for ARC003, ARC007) is provided as median exposure to AR101 and as estimated treatment duration for ongoing studies. 3: Number of subjects as of 15 Jul 2018.

BIW: twice weekly; CSR: clinical study report; RDBPC: randomized double-blind placebo controlled; DBPC: double-blind placebo controlled; DBPCFC: double-blind, placebo-controlled food challenge; EU: European Union; ID:

identification; IDE: initial dose escalation; NA: North America; OL: open-label; OLFC: open-label food challenge; QD: daily; QOD: every other day; QOW: every other week; QW: once weekly; RWPC: real-world peanut challenge; US: United States.

b. Key Elements of Study Design

i. Exclusion criteria for all controlled studies included:

- Pregnant and breastfeeding
- Use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers, or tricyclic antidepressants
- History of severe or life-threatening anaphylaxis or anaphylactic shock within 60 days before screening
- History of eosinophilic esophagitis (EoE), other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (e.g., difficulty swallowing, food "getting stuck"), or recurrent GI symptoms of undiagnosed etiology
- History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension
- Subjects in "build-up phase" of immunotherapy to another allergen (i.e., had not reached maintenance dosing)
- Severe asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] criteria steps 5 or 6)
- Mild or moderate asthma (2007 NHLBI criteria steps 1-4) if uncontrolled or difficult to control as defined by any of the following: forced expiratory volume in the first second of expiration (FEV1) < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted (ARC003 only), with or without controller medications (only for age 6 years or older and able to do spirometry) or inhaled corticosteroids dosing of > 500 µg daily fluticasone (or equivalent inhaled corticosteroids based on NHLBI dosing chart) or 1 hospitalization in the previous year for asthma or emergency department visit for asthma within 6 months before screening
- History of 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, burst oral (IM or IV) steroid course in the previous 3 months before randomization, > 2 burst oral (IM or IV) steroid courses in the previous year of at least 1-week duration

- Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing or DBPCFC when required
- Lack of an available palatable vehicle food to which the subject was not allergic
- Use of any therapeutic antibody (e.g., omalizumab, mepolizumab, reslizumab), any investigational peanut immunotherapy (e.g., oral, sublingual, epicutaneous), or any other immunomodulatory therapy excluding corticosteroids within the previous 6 months
- Development of dose-limiting symptoms in reaction to the placebo part of the screening DBPCFC when required
- Use of other forms of peanut immunotherapy within 6 months before screening
- History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (e.g., cold urticaria, cholinergic urticaria) and hereditary or idiopathic angioedema
- Allergy to oat (ARC003 only; oat flour was an ingredient in the food challenge material used as filler)
- Hypersensitivity to epinephrine and any of the excipients in the product
- Having the same place of residence as another subject in the study (to avoid potential dosing errors)

ii. Dose Regimen

Treatment was initiated at 0.5 mg of AR101 and escalated in increments up to 6 mg at 20 to 30-minute intervals if allergy symptoms were no more than mild in severity. The following day, tolerability of 3 mg was confirmed and then up-dosing was initiated at 3 mg/day. During up-dosing, dose levels were increased incrementally at 2-week intervals (dose escalation approximately every 2 weeks with once daily doses of 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and ending at the maintenance dose of 300 mg/day). Study product doses could be reduced, held, or withheld at investigator discretion for adverse events or allergy symptoms. In the AR101 clinical studies, treatment at 300 mg/day for 2 weeks was included as the last step of up-dosing. However, all data related to exposures of 300 mg/day (i.e., during both up-dosing and maintenance) were combined for analysis.

Initial dosing and initiation of each new dose escalation were conducted under medical supervision at the study sites. Subjects were monitored for at least 90

minutes after completion of each dose escalation, with vital sign measurements and assessment for signs and symptoms of an allergic reaction performed every 30 minutes. Daily dosing continued at home and reactions to study product were recorded in diaries. Study product doses could be reduced, held, or withheld at investigator discretion for adverse events or allergy symptoms.

Reviewer comment: Risk mitigation strategies of note during the premarket clinical trials included administration of IDE and initiation of up-dosing under medical supervision.

iii. Adverse Event Assessment

Adverse events including allergy symptoms and use of concomitant medications were recorded from subject diaries, parent/caregiver interviews and clinic visits. The two safety databases (controlled population and integrated) were assessed independently to allow for separate analysis of controlled data.

Prespecified adverse events of special interest (AESI) included:

- Systemic allergic reaction/anaphylaxis - All systemic allergic reactions were initially recorded under the umbrella term “anaphylaxis,” the most severe reaction on the spectrum of allergic reactions, even when the severity was mild or moderate. Anaphylaxis (Medical Dictionary for Regulatory Activities [MedDRA] preferred term ‘anaphylactic reaction’) was defined in the protocols as a severe, potentially life-threatening systemic hypersensitivity reaction characterized by rapid onset with life-threatening airway, breathing, or circulatory problems that are usually, although not always, associated with skin and mucosal changes [7, 16-18].

To enable characterization of the entire spectrum of systemic allergic reactions accurately, a modified version of the Sampson criteria for determining anaphylaxis was used to include all potential cases of multiorgan allergic reactions for evaluation, independent of severity. This allowed study investigators to diagnose all systemic allergic reaction events as anaphylaxis even though the events may not have been severe or life-threatening as required by the Second Symposium on the Definition and Management of Anaphylaxis and follow-up International Consensus (ICON) guidelines [18, 19]. In study ARC003, an independent adjudication committee reviewed blinded reports of serious adverse events and other events of clinical interest to assess the seriousness, severity, causality, and diagnosis per protocol definitions.

In addition, in study ARC003, a prespecified modified standardized MedDRA query (SMQ) search was conducted to identify additional cases of systemic allergic reaction that were not reported as anaphylaxis by investigators, to further ensure that potential anaphylaxis events were identified. A modified SMQ search of the safety data identified adverse

events that occurred together within a 2-hour interval and involved 2 or more organ systems.

The five-point Consortium of Food Allergy Research (CoFAR) grading scale[20] was used for coding the severity of allergic reactions, except for systemic allergic reactions. The 3-point European Academy of Allergy and Clinical Immunology (EAACI) grading scale[17] was used for grading the severity of systemic allergic reactions, and the multiple symptoms associated with these reactions were rated individually on the CoFAR scale.

- Chronic/recurrent GI adverse events including eosinophilic esophagitis (EoE) – Investigators evaluated as AESI development of recurrent GI symptoms or disease, including eosinophilic esophagitis (EoE), other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (eg, difficulty swallowing, food “getting stuck”), or recurrent GI symptoms of undiagnosed etiology. These AEs were assessed with specific attention to events leading to discontinuation of the study product.

Of note, biopsy-confirmed EoE is reported to occur in 2.5% to 7.3% of patients during treatment of food allergy with oral immunotherapy (OIT) [22], although symptoms usually resolve upon cessation of OIT.. Subjects who developed biopsy-documented EoE were discontinued from trials.

- Use of epinephrine: defined as ≥ 1 dose within a 2-hour period.

A safety monitoring committee met periodically to review accruing safety data. The committee members were not involved in study conduct.

c. Results

i. Demographics

Subjects from North America (United States, Canada) and Europe (Germany, Spain, Great Britain, Ireland, Sweden, Italy, Denmark, and the Netherlands) were enrolled in AR101 studies, with approximately 80% of subjects from the United States.

The median age was 9.0 years for both treatment groups in the controlled population and for the integrated safety population. Most subjects were aged 4 to 11 years (65.4% AR101, 69.5% placebo in the controlled population, 65.6% AR101 in the once daily in the integrated safety population), and white (75.7%, 71.9%, 76.0%). The proportion of subjects who were Hispanic or Latino was similar (6.8%, 7.9%, 7.4%).

ii. Nonserious Treatment-Emergent AEs – Controlled Population

Treatment-emergent nonserious AEs that occurred more than 5% more commonly in the treatment group than in the placebo group are listed in the table below:

Table 2 - Treatment-Emergent Adverse Events With Incidence in the AR101 Group at Least 5% Higher Over Placebo (Controlled Population) (From STN 125696/0 Module 2.7.4 Integrated Summary of Safety, Table 14)

Preferred Term	Combined IDE and Up-Dosing		Study ARC003 300 mg/day (maintenance phase)	
	AR101 (N = 709)	Placebo (N = 292)	AR101 (N = 310)	Placebo (N = 118)
Subjects with at least 1 adverse event	694 (97.9%)	269 (92.1%)	270 (87.1%)	94 (79.7%)
Abdominal pain	363 (51.2%)	62 (21.2%)	46 (14.8%)	7 (5.9%)
Throat irritation	296 (41.7%)	56 (19.2%)	43 (13.9%)	11 (9.3%)
Pruritus	252 (35.5%)	68 (23.3%)	45 (14.5%)	14 (11.9%)
Vomiting	262 (37.0%)	49 (16.8%)	50 (16.1%)	14 (11.9%)
Cough	229 (32.3%)	68 (23.3%)	61 (19.7%)	22 (18.6%)
Nausea	248 (35.0%)	42 (14.4%)	45 (14.5%)	8 (6.8%)
Urticaria	206 (29.1%)	59 (20.2%)	63 (20.3%)	17 (14.4%)
Abdominal pain upper	214 (30.2%)	43 (14.7%)	41 (13.2%)	9 (7.6%)
Abdominal discomfort	183 (25.8%)	39 (13.4%)	19 (6.1%)	7 (5.9%)
Oral pruritus	190 (26.8%)	24 (8.2%)	39 (12.6%)	5 (4.2%)
Sneezing	151 (21.3%)	37 (12.7%)	33 (10.6%)	5 (4.2%)
Throat tightness	109 (15.4%)	10 (3.4%)	20 (6.5%)	0
Paraesthesia oral	102 (14.4%)	16 (5.5%)	23 (7.4%)	2 (1.7%)
Wheezing	87 (12.3%)	21 (7.2%)	19 (6.1%)	10 (8.5%)
Anaphylactic reaction	67 (9.4%)	11 (3.8%)	27 (8.7%)	2 (1.7%)
Tongue pruritus	68 (9.6%)	10 (3.4%)	10 (3.2%)	1 (0.8%)
Lip pruritus	66 (9.3%)	7 (2.4%)	12 (3.9%)	1 (0.8%)
Dyspnoea	54 (7.6%)	6 (2.1%)	17 (5.5%)	1 (0.8%)
Ear pruritus	43 (6.1%)	3 (1.0%)	7 (2.3%)	0
Chest discomfort	41 (5.8%)	2 (0.7%)	8 (2.6%)	0

Reviewer Comment: The imbalance noted for these AEs is likely a manifestation of subjects reacting to the peanut allergen in the product; in particular, hypersensitivity manifesting in the gastrointestinal (GI) tract. Such symptoms would be expected for an allergenic product that is being ingested. Incidence of each of these AEs dropped substantially during the maintenance period, but still continued to exceed incidence noted in the placebo group.

iii. Serious treatment-emergent AEs – Controlled Population

Treatment-emergent SAEs occurring in the controlled population are summarized in the table below:

Table 3: Serious Adverse Events, Fatal and Non-Fatal (Controlled Population)

(From STN 125696.0, Module 2.7.4, Table 26)

System Organ Class (SOC) Preferred Term (PT)	Combined IDE and Up-Dosing		Study ARC003 300 mg/day	
	AR101 (N = 709)	Placebo (N = 292)	AR101 (N = 310)	Placebo (N = 118)
Subjects with at least 1 serious adverse event	6 (0.8%)	2 (0.7%)	4 (1.3%)	1 (0.8%)
Immune system disorders	2 (0.3%)	0	1 (0.3%)	0
Anaphylactic reaction ¹	2 (0.3%)	0	1 (0.3%)	0
Infections and infestations	1 (0.1%)	1 (0.3%)	2 (0.6%)	0
Appendicitis	0	1 (0.3%)	0	0
Pneumonia mycoplasmal	1 (0.1%)	0	0	0
Gastroenteritis	0	0	1 (0.3%)	0
Gastroenteritis viral	0	0	1 (0.3%)	0
Pharyngitis streptococcal	0	0	1 (0.3%)	0
Respiratory, thoracic, and mediastinal disorders	2 (0.3%)	0	0	0
Asthma	2 (0.3%)	0	0	0
Injury, poisoning, and procedural complications	0	1 (0.3%)	1 (0.3%)	1 (0.8%)
Craniocerebral injury	0	1 (0.3%)	0	0
Concussion	0	0	1 (0.3%)	0
Humerus fracture	0	0	0	1 (0.8%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.1%)	0	0	0
Acute lymphocytic leukaemia	1 (0.1%)	0	0	0

1. Systemic allergic reactions (any severity), including anaphylaxis (severe).

The incidence of serious adverse events (SAEs) was similar between treatment groups (0.8% AR101 and 0.7% placebo during initial dose escalation and up-dosing combined; 1.3% and 0.8% during 300 mg/day dosing). No subject had a serious adverse event during initial dose escalation. 2 PTs were reported in more than 1 subject: systemic allergic (anaphylactic) reaction designated as 'serious' was reported in 3 subjects (2 during up-dosing and 1 during 300 mg/day dosing), and asthma was reported in 2 subjects during up-dosing.

A single death was reported in AR101 clinical studies. A 13-year-old female placebo recipient in ARC007 sustained a craniocerebral injury in a road traffic accident on Day 25 and died on the same day.

iv. Treatment-Emergent AEs – Integrated Safety Population

Treatment-emergent AEs with at least 10% incidence overall are listed in the table below. Of note, subjects who received a 300 mg dose of AR101 at any time, for any duration, are represented in the column headed '300 mg/day (any wks).'

Table 4: Treatment-Emergent Adverse Events With at Least 10% Incidence Overall (Integrated Safety Population) (adapted from STN 125696.0, Module 2.7.4, Table 15)

Preferred Term	IDE (N = 812)	Up-Dosing (N = 794)	300 mg/day (N = 661)	Overall (N = 812)
Subjects with at least 1 adverse event	419 (51.6%)	769 (96.9%)	541 (81.8%)	802 (98.8%)
Abdominal pain	166 (20.4%)	346 (43.6%)	92 (13.9%)	418 (51.5%)
Throat irritation	66 (8.1%)	303 (38.2%)	105 (15.9%)	348 (42.9%)
Vomiting	26 (3.2%)	282 (35.5%)	107 (16.2%)	343 (42.2%)
Cough	20 (2.5%)	259 (32.6%)	129 (19.5%)	327 (40.3%)
Pruritus	60 (7.4%)	240 (30.2%)	90 (13.6%)	310 (38.2%)
Nausea	72 (8.9%)	249 (31.4%)	89 (13.5%)	304 (37.4%)
Urticaria	31 (3.8%)	222 (28.0%)	128 (19.4%)	287 (35.3%)
Abdominal pain upper	14 (1.7%)	237 (29.8%)	70 (10.6%)	262 (32.3%)
Abdominal discomfort	33 (4.1%)	189 (23.8%)	68 (10.3%)	227 (28.0%)
Oral pruritus	51 (6.3%)	191 (24.1%)	60 (9.1%)	223 (27.5%)
Rhinorrhoea	17 (2.1%)	166 (20.9%)	79 (12.0%)	220 (27.1%)
Upper respiratory tract infection	3 (0.4%)	177 (22.3%)	94 (14.2%)	219 (27.0%)
Headache	10 (1.2%)	165 (20.8%)	83 (12.6%)	208 (25.6%)
Pyrexia	2 (0.2%)	141 (17.8%)	90 (13.6%)	200 (24.6%)
Nasal congestion	14 (1.7%)	158 (19.9%)	58 (8.8%)	193 (23.8%)
Sneezing	29 (3.6%)	154 (19.4%)	51 (7.7%)	191 (23.5%)
Oropharyngeal pain	5 (0.6%)	117 (14.7%)	63 (9.5%)	153 (18.8%)
Rash	14 (1.7%)	109 (13.7%)	45 (6.8%)	146 (18.0%)
Throat tightness	19 (2.3%)	109 (13.7%)	31 (4.7%)	135 (16.6%)
Nasopharyngitis	1 (0.1%)	92 (11.6%)	46 (7.0%)	121 (14.9%)
Diarrhoea	9 (1.1%)	98 (12.3%)	35 (5.3%)	120 (14.8%)
Paraesthesia oral	13 (1.6%)	100 (12.6%)	33 (5.0%)	120 (14.8%)
Wheezing	5 (0.6%)	95 (12.0%)	39 (5.9%)	120 (14.8%)
Anaphylactic reaction	5 (0.6%)	71 (8.9%)	57 (8.6%)	119 (14.7%)
Dyspnoea	3 (0.4%)	62 (7.8%)	38 (5.7%)	91 (11.2%)
Viral infection	1 (0.1%)	62 (7.8%)	39 (5.9%)	91 (11.2%)
Lip pruritus	5 (0.6%)	69 (8.7%)	30 (4.5%)	87 (10.7%)
Flushing	21 (2.6%)	60 (7.6%)	17 (2.6%)	82 (10.1%)
Tongue pruritus	13 (1.6%)	71 (8.9%)	24 (3.6%)	82 (10.1%)

Reviewer comment: As in the controlled population, commonly reported AEs in the integrated safety population were generally related to hypersensitivity. Overall, substantially more AEs were reported during up-dosing than IDE.

v. Serious treatment-emergent AEs – Controlled Population

Treatment-emergent SAEs occurring in the controlled population are summarized in the table below:

Table 5: Treatment-Emergent Serious Adverse Events (Integrated Safety Population) (From STN 125696.0, Module 2.7.4, Table 27)

System Organ Class Preferred	IDE (N = 812)	Up-Dosing	300 mg/day (any)	Overall (N =
Subjects with at least 1 serious adverse	0	6 (0.8%)	8 (1.2%)	13 (1.6%)
Immune system disorders	0	2 (0.3%)	2 (0.3%)	4 (0.5%)
Anaphylactic reaction	0	2 (0.3%)	2 (0.3%)	4 (0.5%)
Infections and infestations	0	1 (0.1%)	3 (0.5%)	4 (0.5%)
Gastroenteritis	0	0	1 (0.2%)	1 (0.1%)
Gastroenteritis viral	0	0	1 (0.2%)	1 (0.1%)
Pharyngitis streptococcal	0	0	1 (0.2%)	1 (0.1%)
Pneumonia mycoplasmal	0	1 (0.1%)	0	1 (0.1%)
Streptococcal infection	0	0	1 (0.2%)	1 (0.1%)
Injury, poisoning, and procedural complications	0	0	2 (0.3%)	2 (0.2%)
Concussion	0	0	1 (0.2%)	1 (0.1%)
Humerus fracture	0	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic, & mediastinal	0	2 (0.3%)	0	2 (0.2%)
Asthma	0	2 (0.3%) [1]	0	2 (0.2%)
Gastrointestinal disorders	0	0	1 (0.2%)	1 (0.1%)
Abdominal pain	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders	0	0	1 (0.2%)	1 (0.1%)
Dehydration	0	0	1 (0.2%)	1 (0.1%)
Neoplasms benign, malignant, and unspecified (including cysts	0	1 (0.1%)	0	1 (0.1%)
Acute lymphocytic leukaemia	0	1 (0.1%)	0	1 (0.1%)

In addition to the 4 AR101-treated subjects in ARC003 with serious adverse events at 300 mg/day in the controlled population, an additional 4 subjects experienced 1 or more treatment-emergent serious adverse event during dosing with 300 mg/day during follow-on studies. At least two of these events, 1 event of moderate systemic allergic reaction, and 1 event of moderate abdominal pain, are at least possibly related to treatment. Of note, all 4 subjects continued study treatment after temporary dose interruption.

vi. **Adverse Events of Special Interest – Systemic allergic reactions/anaphylactic reactions**

In the controlled population during initial dose escalation and up-dosing combined, 81 anaphylactic reactions by any trigger (study product, food allergen, other allergen) were reported in 67 subjects (9.4%) in the AR101 group and 11 were reported in 11 subjects (3.8%) in the placebo group. During 300 mg/day maintenance dosing in ARC003, 33 anaphylactic reactions were reported in 27 subjects (8.7%) in the AR101 group and 2 were reported in 2 subjects (1.7%) in the placebo group. Most anaphylactic reactions (>80%) in the AR101 group were considered triggered by study product.

Three subjects in the controlled population were reported to have sustained anaphylactic reactions designated as 'serious,' 2 (0.3%) during up-dosing and 1 (0.3%) during 300 mg/day dosing in ARC003. Of note, these events were not termed 'anaphylaxis.'

Discontinuations due to anaphylactic reactions occurred in 11 AR101 subjects (1.6%) during initial dose escalation and up-dosing combined. No subjects in the placebo group discontinued due to an anaphylactic reaction.

Results of the evaluation of anaphylactic reactions for the integrated safety population were consistent with the results for the controlled population. A total of 169 anaphylactic reactions were reported overall in 118 subjects and most were reported during up-dosing (85 events, 71 subjects), followed by 300 mg/day dosing (79 events, 56 subjects) and initial dose escalation (5 events, 5 subjects).

Among the 169 anaphylactic reactions that occurred in the integrated safety population, 5 (3%) occurred during IDE, 85 (50%) occurred during up-dosing, and 79 (47%) occurred during 300 mg/day maintenance dosing.

Overall, 14 subjects (1.7%) treated with AR101 discontinued due to anaphylactic reaction.

Most anaphylactic reactions were nonserious, including events reported as 'anaphylaxis.' Four subjects had a serious anaphylactic reaction: 2 (0.3%) during up-dosing and 2 (0.3%) during all 300 mg/day dosing. 10 subjects sustained events termed 'anaphylaxis;' of these, one was evaluated as an SAE.

Reviewer comment: The boxed warning, and *Warnings and Precautions* section 5.1, of the proposed label includes the risk of systemic allergic reactions, including anaphylaxis. In addition, FDA will require a REMS with elements to assure safe use to mitigate the risk of systemic allergic reactions. (Please see section 5 of this review memorandum for discussion of REMS.)

vii. Adverse Events of Special Interest – Chronic/recurrent GI Adverse Events including EoE

In the controlled population, 55 subjects (7.8%) in the AR101 group and 3 subjects (1.0%) in the placebo group had 1 or more adverse events in the GI disorders system organ class that led to discontinuation of study product. Of these 55 subjects, 36 subjects in the AR101 group and no subjects in the placebo group discontinued from the study due to chronic or recurrent GI adverse events. All subjects who discontinued due to chronic or recurrent GI adverse events had GI adverse events during initial dose escalation and up-dosing; no subjects discontinued due to chronic/recurrent GI adverse events during 300 mg/day dosing in ARC003.

For subjects in the controlled population who discontinued from the study due to chronic or recurrent GI events, the most common chronic or recurrent GI adverse events (> 15% of subjects during combined period of IDE and up-dosing) were abdominal pain (27 subjects, 75%) nausea and vomiting (25 subjects each, 69.4%), oral pruritus (12 subjects, 33.3%), abdominal discomfort and upper abdominal pain (11 subjects each, 30.6%), oral paresthesia (7 subjects, 19.4%), and diarrhea (6 subjects, 16.7%).

In the integrated safety population, 62 subjects (7.6%) had 1 or more adverse events in the GI disorders system organ class that led to discontinuation of study product. Of these, 36 subjects (58%) discontinued from the study due to chronic or recurrent GI adverse events. Among these 36 subjects, 20 subjects had at least 1 GI adverse event during initial dose escalation and 36 subjects during up-dosing. All subjects discontinued during up-dosing.

Among the 36 patients in the integrated safety population who discontinued due to chronic or recurrent GI adverse events, the most common events (> 15% in any period) reported were abdominal pain (17 subjects, 47.2% during IDE; 24 subjects, 66.7% during up-dosing), nausea (7 subjects, 19.4% during IDE; 23 subjects, 63.9% during up-dosing), vomiting (25 subjects, 69.4% during up-dosing), oral pruritus (5 subjects, 13.9% during IDE; 10 subjects, 27.8% during up-dosing), oral paresthesia (2 subjects, 5.6% during IDE; 6 subjects, 16.7% during up-dosing), abdominal discomfort (1 subject, 2.8% during IDE; 11 subjects, 30.6% during up-dosing), and upper abdominal pain (1 subject, 2.8% during IDE; 30.6% during up-dosing).

EoE was diagnosed in 3 of 692 AR101 recipients in the controlled population (0.4%), all during up-dosing and all in the AR101 group. In the Integrated Safety Population, EoE was reported in an additional 2 recipients of AR101, for a total of 5 cases in 812 AR101 recipients, yielding an overall incidence of 0.5%. All cases were reported during the up-dosing period.

Reviewer comment: PALFORZIA is contraindicated in patients with a history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease. Additionally, Sections 5.4 and 5.5 of 'Warnings and Precautions' in the proposed label indicate that gastrointestinal adverse reactions should prompt discontinuation and consideration of a diagnosis of eosinophilic esophagitis.

viii. **Adverse Events of Special Interest – Epinephrine Use**

Epinephrine use was defined as ≥ 1 dose within a 2-hour period.

74 subjects (10.4%) in the AR101 group reported 94 episodes of epinephrine use during the IDE/up-dosing period; of these, 36 episodes (38.3%) occurred at the study site, and 58 (61.7%) happened at a location other than the study site. 14 subjects (4.8%) in the placebo arm reported 14 episodes of epinephrine use

during IDE/up-dosing, including 2 episodes (14.3%) occurring at the study site, and 12 episodes (85.7%) occurring at a location other than the study site. 29 episodes of epinephrine use were experienced by 25 subjects of the AR101 group (8.1%) during 300 mg/day dosing; of these 29 episodes, 3 (10.3%) occurred at the study site, and 26 (89.7%) happened at a location other than the study site. 4 episodes occurred in 4 subjects in the placebo arm group (1.7%) during 300 mg/day dosing.

The most commonly reported reason for epinephrine use for subjects during the IDE/up-dosing period was anaphylactic reaction (43/74 treated subjects, 58%; 9/14 placebo arm subjects, 64%). Anaphylactic reaction was also the most common reason for epinephrine use during 300 mg/day dosing, reported by 19/25 subjects (76%) in the treatment arm and 2/4 subjects (50%) in the placebo arm. Of note, the 94 occurrences of epinephrine use during IDE/up-dosing were usually associated with events and symptoms of Grade 1 or 2 severity (85 events, 90.5% AR101; 14 events, 100% placebo arm). Epinephrine use was also usually associated with Grade 1 or 2 severity events during 300 mg/day dosing (28/29 events, 96.6% in the AR101 arm, and 4/4 events, 100% in the placebo arm).

In the integrated safety population, 124 of 812 subjects (15.3%) used epinephrine at least once; 94 subjects reported epinephrine use during the IDE/up-dosing period, and 55 subjects reported epinephrine use during 300 mg/day dosing (subjects reporting in both periods could be counted once for each period). A total of 186 episodes of epinephrine use were reported. 16 (8.6%) of these episodes were reported during IDE, all of which occurred at a location away from the study site. 97 episodes (52%) were reported during up-dosing. Among these 97 events were 30 (30.9%) which occurred at the study site, and 67 (69.1%) which occurred at a location away from the study site. 73 of the 186 episodes (39%) were reported during 300 mg/day dosing. Among these 73 events were 6 (8.2%) which occurred at the study site, and 67 (91.8%) which occurred at a location away from the study site.

Anaphylactic reaction was the most common reason for epinephrine use by subjects in the integrated safety population during the IDE/up-dosing period (50/94 subjects, 53%) as well as during 300 mg/day dosing (45/55 subjects, 82%). As in the controlled population, most epinephrine use occurred during events of Grade 1 or 2 severity; this was true in 15/16 events during IDE (74%), 86/97 events during up-dosing (88.6%), and 69/73 events during 300 mg/day dosing (94.5%).

Reviewer comment: The boxed warning, and *Warnings and Precautions* section 5.1 of the proposed label includes prescribing epinephrine auto-injector, and instructing and training patients on its appropriate use. In addition, FDA will require a REMS with elements to assure safe use so that PALFORZIA is only dispensed to patients with documentation of safe use conditions, requiring that

patients are informed of the need to carry epinephrine at all times. (Please see section 5 of this review memorandum for discussion of REMS.)

viv. ARCR008 Preliminary Safety Data

As of the data cutoff date of July 15, 2018, the study had enrolled 339 subjects (207 subjects aged 4-11 years, 120 subjects aged 12-17 years and 11 subjects aged 18-55 years) with an overall median exposure of 103 days.

The most common adverse events were abdominal pain (72 subjects, 21.2%), throat irritation (44 subjects, 13.0%), urticaria and pruritus (43 subjects, 12.7% each), abdominal discomfort and cough (42 subjects, 12.4% each), and vomiting (40 subjects, 11.8%). Systemic allergic reaction (MedDRA preferred term 'anaphylactic reaction') were reported in 19 subjects (5.6%). Two subjects have experienced serious adverse events (appendicitis, salmonella bacteremia).

Twenty subjects (5.9%) had a total of 23 adverse events of systemic allergic reaction and epinephrine was used in 12 of 23 events. AR101 was the most common trigger of systemic allergic reaction (16 episodes), followed by peanut or peanut-containing food (4 episodes), other food allergen (2 episodes) and unknown (1 episode). No event was assessed as anaphylaxis (severe anaphylactic reaction) by investigators.

Four subjects experienced EoE, including 2 subjects diagnosed after the cutoff date of July 15, 2019.

4. Pharmacovigilance Plan (Version 1, dated 12/21/2018)

Safety issues identified by the sponsor as well as the sponsor's proposed risk mitigation strategies are summarized in the table below:

Table 6: Sponsor-Proposed Pharmacovigilance Plan (adapted from sponsor's Pharmacovigilance plan (PVP), Section 1.16 of 125696/0)

	Safety Concern	Pharmacovigilance Action
1	Anaphylaxis and Systemic Allergic Reactions (identified risk)	<ul style="list-style-type: none"> - Routine PV with hypersensitivity-specific follow-up questionnaires and summary analysis in aggregate reports - REMS - Boxed warning in PI advising observation period during IDE as well as other risk mitigation measures; patient medication guide - Additional safety information to be derived from long term follow up of open-label study ARC008, as well as other ongoing studies with the product
2	Eosinophilic Esophagitis (identified risk)	- Routine PV with EoE-specific

		follow-up questionnaires and summary analysis in aggregate reports - History of EoE labeled in PI as a Contraindication; risk of EoE labeled in PI under 'Warnings and Precautions' - Additional safety information to be derived from long term follow up of open-label study ARC008, as well as other ongoing studies with the product
3	Concomitant medications potentiating/inhibiting the effects of epinephrine (potential risk)	- Routine PV
4	Severe or uncontrolled asthma (potential risk)	- Routine PV - Ongoing uncontrolled asthma labeled in PI as a Contraindication; labeling in PI warning against use during acute exacerbation or in patients with history of recurrent exacerbations
5	Use in children < 4 years of age (missing information)	- Product indication excluding use in this population - Routine PV - Additional safety information to be derived from ARC005, an ongoing study of children aged 1 year to <4 years
6	Use in adults >55 years of age (missing information)	- Product indication excluding use in this population - Routine PV
7	Use in patients who may be pregnant or nursing (missing information)	- Routine PV - Pregnancy registry - Label states that this therapy is not recommended for this patient population

The sponsor describes "routine pharmacovigilance" as "adverse reactions reporting and signal detection." The sponsor states that "Individual Case Safety Reports (ICSRs) from postmarketing sources (spontaneous, solicited, literature, and regulatory authorities) [will be] collected, investigated, and submitted to the FDA according to the timelines defined in 21 CFR 600.80." Routine pharmacovigilance activities will include expedited reporting to FDA of serious and unexpected AEs as well as development and submission of Periodic Adverse Experience Reports in accordance with FDA regulations. The sponsor also indicates a plan to conduct follow-up questionnaires for patients who report anaphylactic reactions or EoE associated with use of the product during the postmarket period; additional information on the design of these questionnaires or parameters under which they will be used was not provided.

In addition to routine PV, the sponsor proposes several other elements as part of the PVP. The Risk Evaluation and Mitigation Strategy (REMS) will be discussed in section 5.

Multiple studies are underway or planned to expand the product indication or for long-term follow-up of treated subjects; additional safety data can be derived from these studies.

- Studies ARC004 and ARC011 are underway as extensions to the completed pivotal studies.
- As previously noted, ARC008 is a phase 3, international, open-label, long-term safety study of an AR101 regimen in peanut-allergic children and adults. Subjects entering ARC008 originate from a current or completed AR101 clinical study or any future clinical study that identifies ARC008 as a potential post study option in the parent study protocol. Subjects in the current protocol may have received active drug or placebo in the parent study. The sponsor plans a protocol amendment to extend the safety follow-up period to 3 years on a subset of the subjects in order to obtain information on safety of product use during the maintenance period. The sponsor predicts that approximately 1100 subjects will ultimately be enrolled in this study.
- The sponsor has initiated clinical trial ARC005, "Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON)." This is a phase 3, international, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AR101 in approximately 140 peanut-allergic children aged 1 to < 4 years. This study will be conducted as a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR).
- Finally, the sponsor plans to establish a pregnancy registry as a Postmarket Commitment (PMC) to monitor use and safety of AR101 during pregnancy. Section 8.1 of the proposed label acknowledges the lack of data on the risks of Palforzia in pregnant women and highlights the fact that Palforzia can cause anaphylaxis in pregnant women, which could result in significant risk in a fetus. The planned post-marketing pregnancy registry is currently in development; a study concept was submitted describing a registry that will enroll subjects who were exposed to AR101 during pregnancy identified via spontaneous reporting. The sponsor indicates that subjects will be contacted and relevant baseline information will be collected, with subsequent follow up to obtain information concerning pregnancy outcomes. The registry will continue enrolling patients until 72 qualifying patients are enrolled or until 5 years after Palforzia is commercially available. The sponsor indicates that the registry will be ready to admit patients by the time of marketing. A yearly summary of data derived from the registry will be prepared and filed with the aggregate report following the cut-off date. Milestone dates include

submission of the final protocol by 28 Feb 2020, study completion by 01 Jan 2025, and submission of the final study report by 30 Jan 2026.

Reviewer comment: Available data do not suggest a safety concern that needs to be further assessed in a postmarketing study in the CBER Sentinel Program, or a postmarketing requirement (PMR) safety study under FDAAA. Pregnancy risk will be assessed with the PMC as described above.

5. Risk Evaluation and Mitigation Strategy (REMS)

Systemic allergic reactions including anaphylaxis are serious adverse events that occurred after patients received AR101. In the controlled population, during IDE and up-dosing combined, 9.4% of subjects taking PALFORZIA reported systemic allergic reactions while 3.8% of subjects in the placebo group did. Patients using AR101 are ingesting a substance to which they have a known hypersensitivity. Use of this product was found during the clinical trials to be associated with systemic allergic reactions of all levels of severity, up to and including anaphylaxis, an AE that can potentially result in death. Risk mitigation strategies employed during the premarket trials involved: a) administration of the product during IDE and initiation of up-dosing level only under the controlled conditions of the study site, where subjects were observed for signs/symptoms of allergic reaction for at least 90 minutes and could be readily treated, b) ready access to epinephrine in the event of severe allergic reaction, c) instructions to subjects admonishing them to continue peanut avoidance, and d) a controlled administration plan within which a higher level dose of the product was only available to subjects after they had demonstrated tolerance to the previous lower dose.

During the review of this BLA, it was found that the sponsor's initial proposed risk mitigation strategies for systemic allergic reactions, which consisted of a boxed warning as well as a patient wallet card, medication guide, physician attestation of competence in treating systemic allergic reactions, and distribution controls, were not adequate to mitigate this risk. Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505 1(a)]. For further discussion of the determination that a REMS is necessary; please see the OVRREMS Memorandum and the CDER/Division of Risk Management (DRISK) review memorandum. To ensure that the benefits of Palforzia outweigh the risks of systemic allergic reactions including anaphylaxis, it was determined that a REMS that includes elements to assure safe use (ETASU) is necessary, and the applicant was notified on September 6, 2019, and asked to submit a REMS.

The goal for the REMS is to mitigate the risk of anaphylaxis associated with Palforzia by:

1. Ensuring that healthcare providers who prescribe and healthcare settings that dispense and administer PALFORZIA are educated on the following:

- a. the risk of anaphylaxis associated with the use of PALFORZIA
 - b. the Initial Dose Escalation and first dose of each Up-Dosing level must only be administered to patients in a healthcare setting equipped to monitor patients, and to identify and manage anaphylaxis.
2. Ensuring that the Initial Dose Escalation and the first dose of each Up-Dosing level of PALFORZIA are only provided to certified healthcare settings.
3. Ensuring that PALFORZIA is only dispensed and administered to patients who are informed of the need to have injectable epinephrine immediately available at all times, the need for monitoring after the Initial Dose Escalation and first dose of each Up-Dosing level and the need for continued dietary peanut avoidance by enrolling in the PALFORZIA REMS Program.

Negotiations are underway to determine details of the REMS requirements and REMS materials. An assessment plan will be in place and will include metrics to assess the REMS. Please see the final version of the REMS Document and REMS Materials submitted by the applicant for the agreed-upon elements of the PALFORZIA REMS.

The sponsor will submit REMS assessments to FDA at 6 months, 12 months, and then annually thereafter.

6. Integrated Risk Assessment

Limitations of the studies in the clinical safety database include the wide variety of inclusion and exclusion criteria and the use of DBPCFC, neither reflecting the expected real-world use of the product. Of note, oral food challenges were not required for entry into open-label follow-on studies (ARC004, ARC008, and ARC011). The studies were underpowered to adequately determine the effect of treatment on mortality and serious outcomes, e.g., hospitalizations related to peanut allergy. Additionally, limited long-term follow up information precludes adequate characterization of the safety profile during the maintenance phase of dosing. Study ARC007 did not include a maintenance phase; subjects reached the daily dose of 300 mg Palforzia and were discharged from the study. Finally, the sponsor's decision to allow systemic allergic reaction events to be coded as anaphylaxis even though the events may not have been severe or life-threatening further complicated the evaluation of anaphylaxis.

Available data, including data contained in the current submission, indicate Palforzia may decrease the risk of systemic allergic reaction with accidental exposure to peanuts in sensitized individuals. However, use of the product itself may increase the risk of systemic allergic reactions in treated individuals. The premarket clinical trial data showed that 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. A substantial number of these reactions were documented during the clinical trials, despite trial conditions designed to minimize the number and risk of these events. Additionally, reactions were reported during all phases of treatment. Given that systemic allergic reactions are potentially life-threatening, implementation of a REMS to ensure that use in the postmarket period only occurs

under conditions similar to those of the clinical trials, together with appropriate labeling, constitutes reasonable risk mitigation. Further characterization of this risk will be possible with additional data from ongoing and planned studies.

Risk of chronic/recurrent GI adverse events including EoE was also demonstrated in the clinical trial data. The sponsor's plan to mitigate this safety issue through labeling that advises patients of this risk and admonishes them to discontinue use as necessary is adequate. As with systemic allergic reactions, further characterization of the risk of chronic/recurrent GI adverse events including EoE will be possible with additional data from ongoing and planned studies.

Additional information regarding the sponsor's plans for routine pharmacovigilance for all identified and potential risks will be sought to ensure compliance with 21 CFR 600.80. The proposed PVP is otherwise adequate.

7. Recommendations

- DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP. DE will communicate with the sponsor to ensure that adverse event reporting will be conducted as required under 21 CFR 600.80. Periodic safety reports should be submitted quarterly for three years after licensure, and annually thereafter, and include details of the potential risks and missing information identified in this safety review.
- OBE/DE supports the establishment of a post-marketing commitment for the pregnancy registry described by the sponsor.
- In addition, the risk of systemic allergic reactions necessitates a REMS. DE recommends a REMS with elements to assure safe use to mitigate the risk of systemic allergic reactions; comprised of healthcare setting and pharmacy certification; patient monitoring after administration of IDE and the first dose of each up-dosing level; documentation of safe use conditions requiring that patients are informed of the need to carry epinephrine and the need for continued dietary peanut avoidance. OBE/DE will review REMS assessments at 6 months, 12 months, and then annually thereafter. Negotiations are underway to finalize the details of the REMS.
- Available data do not suggest a safety concern that needs to be further assessed in a postmarketing study in the CBER Sentinel Program, or a postmarketing requirement (PMR) safety study under FDAAA.

References:

1. Cashdan, E., *A sensitive period for learning about food*. Hum Nat, 1994. **5**(3): p. 279-91.
2. Farrow, C. and J. Blissett, *Stability and continuity of parentally reported child eating behaviours and feeding practices from 2 to 5 years of age*. Appetite, 2012. **58**(1): p. 151-6.
3. Kemp, S.F. and R.F. Lockey, *Anaphylaxis: a review of causes and mechanisms*. J Allergy Clin Immunol, 2002. **110**(3): p. 341-8.
4. Fallon, A.E., P. Rozin, and P. Pliner, *The child's conception of food: the development of food rejections with special reference to disgust and contamination sensitivity*. Child Dev, 1984. **55**(2): p. 566-75.
5. Sicherer, S.H. and H.A. Sampson, *Peanut allergy: emerging concepts and approaches for an apparent epidemic*. J Allergy Clin Immunol, 2007. **120**(3): p. 491-503; quiz 504-5.
6. Brough, H.A., et al., *Dietary management of peanut and tree nut allergy: what exactly should patients avoid?* Clin Exp Allergy, 2015. **45**(5): p. 859-871.
7. Simons, F.E., et al., *World allergy organization guidelines for the assessment and management of anaphylaxis*. World Allergy Organ J, 2011. **4**(2): p. 13-37.
8. Summers, C.W., et al., *Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center*. J Allergy Clin Immunol, 2008. **121**(3): p. 632-638.e2.
9. Sampson, H.A., L. Mendelson, and J.P. Rosen, *Fatal and near-fatal anaphylactic reactions to food in children and adolescents*. N Engl J Med, 1992. **327**(6): p. 380-4.
10. Bock, S.A., A. Munoz-Furlong, and H.A. Sampson, *Further fatalities caused by anaphylactic reactions to food, 2001-2006*. J Allergy Clin Immunol, 2007. **119**(4): p. 1016-8.
11. Bock, S.A., A. Munoz-Furlong, and H.A. Sampson, *Fatalities due to anaphylactic reactions to foods*. J Allergy Clin Immunol, 2001. **107**(1): p. 191-3.
12. Turner, P.J., et al., *Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012*. J Allergy Clin Immunol, 2015. **135**(4): p. 956-63.e1.
13. Turner, P.J., et al., *Fatal Anaphylaxis: Mortality Rate and Risk Factors*. J Allergy Clin Immunol Pract, 2017. **5**(5): p. 1169-1178.
14. Sicherer, S.H., A.W. Burks, and H.A. Sampson, *Clinical features of acute allergic reactions to peanut and tree nuts in children*. Pediatrics, 1998. **102**(1): p. e6.
15. Gupta, R.S., et al., *The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States*. Pediatrics, 2018. **142**(6).
16. Johansson, S.G., et al., *Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003*. J Allergy Clin Immunol, 2004. **113**(5): p. 832-6.
17. Muraro, A., et al., *The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology*. Allergy, 2007. **62**(8): p. 857-71.
18. Simons, F.E., et al., *International consensus on (ICON) anaphylaxis*. World Allergy Organ J, 2014. **7**(1): p. 9.
19. Sampson, H.A., et al., *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*, 2006. **117**(2): p. 391-7.
20. Burks, A.W., et al., *Oral immunotherapy for treatment of egg allergy in children. N Engl J Med*, 2012. **367**(3): p. 233-43.