Summary Basis for Regulatory Action

Date: January 31, 2020

From: Taruna Khurana, PhD, Chair of the Review Committee

BLA STN#: 125696/0

Applicant Name: Aimmune Therapeutics, Inc.

Date of Submission: December 21, 2018

Goal Date: January 31, 2020

Proprietary Name: PALFORZIA

Established Name: Peanut (*Arachis hypogaea*) Allergen Powder-dnfp

Indication: PALFORZIA is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Peanut (*Arachis hypogaea*) Allergen Powder-dnfp is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up Dosing and Maintenance may be continued in patients 4 years of age and older.

PALFORZIA is to be used in conjunction with a peanut-avoidant diet.

Limitation of use: Not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

Recommended Action: The Review Committee recommends approval of this product.

Review Office Signatory Authority:
Marion F. Gruber, Ph.D.
Director, Office of Vaccines Research and Review/CBER

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:
Mary A. Malarkey
Director, Office of Compliance and Biologics Quality/CBER

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the Summary Basis of Regulatory Action (SBRA).

Document title	**Reviewer name, Document date**
CMC Reviews • *CMC (OVRR/DBPAP)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ and OVRR/DBPAP)* • Applicant's Response to Inspectional Observations	 Philippa Hillyer, PhD January 28, 2020 Laura Fontan and Gregory Price, January 02, 2020 Laura Fontan, Gregory Price, Jennifer Bridgewater, MPH, and Philippa Hillyer, PhD, October 08, 2019 Laura Fontan, Gregory Price, Jennifer Bridgewater, MPH, and Philippa Hillyer, PhD, October 08, 2019
Clinical Reviews • *Clinical (OVRR/DVRPA)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO (OCBQ/DIS)*	 Kathleen Hise, MD, January 29, 2020 Adamma Mba-Jonas, MD, MPH, January 26, 2020 Erin McDowell, October 21, 2019
Statistical Reviews • *Clinical data (OBE/DB)* • *Non clinical data (OBE/DB)*	 Lei Huang, PhD, January 02, 2020 Lei Huang, PhD, December 13, 2019
Labeling Review(s) • *APLB (OCBQ/DCM/APLB)* • *Carton and Container Label Review (OVRR/DVRPA)* • *Labeling Review (OVRR/DVRPA)*	 Labeling Review-Oluchi Elekwachi, PharmD, MPH, December 09, 2019 PNR Review-Oluchi Elekwachi, PharmD, MPH, May 21, 2019 Suffix Review-Lisa Stockbridge, PhD, August 06, 2019 Daphne Stewart, January 23, 2020 Taruna Khurana, PhD and Diana Oram, PhD, January 31, 2020
Advisory Committee summary	September 13, 2019

1. Introduction

Aimmune Therapeutics, Inc. submitted a Biologics License Application (BLA) STN 125696 for licensure of peanut allergen powder on December 21, 2018. The proprietary name of the product is PALFORZIA. PALFORZIA is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Peanut (*Arachis hypogaea*) Allergen Powder-dnfp is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up Dosing and Maintenance may be continued in patients 4 years of age and older. The product is for oral administration only and is available in six different dosage strengths (0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg capsules; and a 300 mg sachet).

The active ingredient and the drug substance of PALFORZIA is lightly roasted, partially defatted peanut powder. The drug substance is stored at (b) (4) until the drug product is manufactured. To manufacture the drug product, the drug substance is (b) (4). The drug product powder is packaged in color coded Hydroxypropyl Methylcellulose (HPMC) capsules or foil laminated sachets for the final dosages. The product is emptied out of the capsules or sachets into a semisolid food vehicle of choice for oral administration. Capsules are not intended to be swallowed. Capsules and sachets are stored at 2-8°C. The expiration period is 24 months for capsules and 18 months for sachets.

The PALFORZIA dosing regimen consists of three phases: Initial Dose Escalation, Up-Dosing, and Maintenance. The Initial Dose Escalation has 5 dose levels, from 0.5 mg (Level A) to 6 mg (Level E) and is completed in a single day under medical supervision. The Up-Dosing phase consists of 11 dose levels from 3 mg/day (Level 1) to 300 mg/day (Level 11). The first dose of each Up-Dosing phase is administered under medical supervision, and the remaining doses of that level are administered daily at home by the patient or caregiver for two weeks. Maintenance dosing, likewise, is administered daily at home by the patient or caregiver. Because PALFORZIA is made from defatted roasted peanut powder and may cause anaphylaxis in peanut allergic individuals, the labeling includes a Boxed Warning and a Medication Guide emphasizing the potential risk of anaphylaxis and that injectable epinephrine must be available for immediate use at all times while on PALFORZIA. In addition, PALFORZIA will be available and administered only under a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of anaphylaxis, with elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2. Background

Peanut Allergy

Food allergy affects 15 million people in the United States of whom 6 million are children (1). About 50% of cases of anaphylaxis reported by emergency departments

are due to food allergens. Fatalities due to anaphylaxis from food allergies are estimated at about 100 per year in the United States with most deaths occurring during early adulthood. The most common food allergens causing clinical disease are peanut, tree nuts, milk, egg, soy, wheat, and shellfish.

Peanut allergy is the leading cause of food-induced anaphylaxis. The prevalence of peanut allergy in children in the United States is 1-2% and has increased from 0.4% in 1997 (2). The annual incidence of accidental exposures is over 12% in peanut-allergic children (3). Comorbid conditions such as asthma, cardiovascular disease, mast cell disorders, and concurrent use of certain medications have been reported to be associated with increased severity of peanut-induced allergic reactions (4, 5). The quality of life of food-allergic individuals and their caregivers is often reduced due to social isolation and anxiety regarding accidental ingestion of peanut-containing food. While most children with certain food allergies (such as milk, egg, wheat, and soy) become tolerant by late childhood or adolescence, only 20% of children with peanut allergy outgrow the condition (6).

Currently, peanut allergy treatment is limited to strict peanut avoidance and treating the symptoms of allergic reactions after accidental exposure to peanut allergens - either with immediate injection of epinephrine for suspected or confirmed anaphylaxis or with antihistamines for milder symptoms. There is no licensed immunotherapy treatment option available for peanut allergy.

Regulatory History

Key regulatory milestones in the development of PALFORZIA are listed in Table 1

Table 1: Key Regulatory Activities

Date	Regulatory Milestone
November 15, 2012	Pre-IND meeting
April 10, 2013	Original IND 15463 submission
September 05, 2014	Fast Track designation granted
June 15, 2015	Breakthrough Therapy designation granted
July 9, 2015	End of Phase 2 CMC meeting
July 20, 2015	End of Phase 2 clinical meeting
July 31, 2017	Agreement to revise the primary efficacy endpoint to include only pediatric subjects ages 4 through 17 years
September 26, 2018	Pre-BLA meeting
December 21, 2018	BLA submission
March 13, 2019	BLA 125696 Filed

Date	Regulatory Milestone
September 13, 2019	Allergenic Products Advisory Committee Meeting

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

The drug substance (DS) of PALFORZIA is lightly roasted, (b) (4) defatted peanut flour which is a mixture of proteins (b) (4)

Source Material/Drug Substance Manufacturing Overview

The source material (SM) is manufactured and tested at (b) (4)

Table 2: Source Material Release Tests and Acceptance Criteria

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Drug Product Manufacturing Overview

The drug product (DP) is a powder for oral use that is supplied in pull apart hydroxypropylmethyl cellulose (HPMC) capsules or foil laminated sachets. The DP is manufactured under GMP conditions. For DP manufacturing, dry excipients, as listed in Table 4, (b) (4)

Table 4: Final Formulation of PALFORZIA

Ingredients (function)	(b) (4) **for 0.5 mg dose capsule**	(b) (4) **for 1 mg dose capsule**	(b) (4) **for 10 mg dose capsule**	(b) (4) **for 20 mg dose capsule**	(b) (4) **for 100 mg dose capsule or 300 mg dose sachet**
Peanut (*Arachis hypogaea*) Powder (DS-active component)	(b) (4)				
Microcrystalline cellulose (b) (4)					
Partially pregelatinized maize starch (b) (4)					
Colloidal silicon dioxide (b) (4)					
Magnesium stearate (b) (4)					

The DP manufacturing process involves (b) (4)

(b) (4)

The date of manufacture of DP is defined as the date when the (b) (4)

The commercial batch size for PALFORZIA is listed in Table 5.

Table 5: Commercial Batch Size

Dose Strength	Batch Size (number of units)
0.5 mg capsule	(b) (4)
1 mg capsule	
10 mg capsule	
20 mg capsule	
100 mg capsule	
300 mg sachet	

The applicant has performed manufacturing process performance qualification (PPQ) as per FDA guidelines. Validation was performed for blending and encapsulation using a (b) (4) approach (b) (4) 0.5 mg capsules, (b) (4) of 1 mg and 10 mg capsules (b) (4) of 20 mg and 100 mg capsules. (b) (4)

for the 300 mg dose as described above. All results were within specifications.

Drug Product Packaging Configurations

PALFORZIA comes in three configurations as per the dosing regimen.

- *Initial Dose Escalation*

  0.5 mg, 1 mg, 1.5 mg (one 1 mg capsule and one 0.5 mg capsule), 3 mg (three 1 mg capsules) and 6 mg (six 1 mg capsules) dosages are packaged into blister strips and presented together on one paperboard card. Each

dose is administered in succession under medical supervision on the first day of treatment.

- *Up-Dosing*

  The 3, 6, 12, 20, 40, 80, 120, 160, 200, 240 and 300 mg dosages consist of groups of capsules whose combined dosage strengths equal the respective total dosage or a sachet (for 300 mg only). Each Up-Dosing dosage is provided in two forms:

  - The physician sample doses to be administered under medical supervision come in individual blisters and sachets. The individual blisters and sachets are packaged in cartons. The carton is labeled as "Physician Sample not for sale."
  - The daily dose packs for home use come in a two weeks supply of 15 doses of capsules packaged into two rows of blister strips. The daily dose pack is presented in a tri-folded paperboard card with child resistant features. The two extra doses are demarcated with the statement "extra doses as needed." Sachets are provided in a 15-dose carton.

- *Maintenance*

  300 mg daily dose sachets are provided in cartons containing a 30-day supply for at home daily use.

Drug Product Specifications and Analytical Methods

The analytical methods and their validations and/or qualifications reviewed for the PALFORZIA drug substance and drug product were found to be adequate for their intended use.

The DP lots are released as per the tests and the acceptance criteria listed in Tables 6 and 7 below for the 0.5 mg capsule and 300 mg sachet dosage examples. The release specifications for (b) (4) protein integrity by HPLC for (b) (4) differ for different dosage strengths. Similarly, the specifications for total protein content and content uniformity are also different for each dosage strength. The (b) (4) specification differs for capsules and sachets. The justifications provided for each test and acceptance criteria are acceptable. The specifications are based on compendial methods or statistical analyses of available data.

Table 6: PALFORZIA Release Specifications for 0.5 mg Capsule Dose

Quality Parameters	Analytical Methods/Tests	Acceptance Criteria
Appearance	Visual Examination	White opaque capsule printed with 0.5 mg in gray on cap and Aimmune printed in gray on body. Contains white to off-

Quality Parameters	Analytical Methods/Tests	Acceptance Criteria
		white fine granular powder, may contain clumps.
Identification	(b) (4)	(b) (4)
Protein Integrity	HPLC	(b) (4)
Total Protein Content	Combustion	(b) (4)
Content Uniformity	(b) (4)	(b) (4) .
Deliverable Mass	Gravimetric	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Relative Potency	ELISA	Ara h 1 (b) (4) Ara h 2 (b) (4) Ara h 6 (b) (4)
Microbiological Limits	(b) (4)	(b) (4)
(b) (4)	Test for (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Table 7: PALFORZIA Release Specifications for 300 mg Sachet Dose

Quality Parameters	Analytical Method/Test	Acceptance Criteria
Appearance	Visual Examination	(b) (4) Contains beige fine powder, may contain clumps.
Identification	(b) (4)	(b) (4)
Protein Integrity	HPLC	(b) (4)
Total Protein Content	Combustion (b) (4)	(b) (4)
Content Uniformity	(b) (4)	(b) (4)
Deliverable Mass	Gravimetric	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Relative Potency	ELISA	Ara h 1 (b) (4) Ara h 2 (b) (4) Ara h 6 (b) (4)
(b) (4)	Test for (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Drug Substance and Drug Product Stability

(b) (4)

(b) (4)

Aimmune proposed a shelf life of 24 months for drug product (DP) at 2 to 8°C based on the data from the completed stability studies and ongoing commercial stability studies. The stability data and the trend analyses support a 24-month expiration period for DP capsules and 18 months for DP in sachets when stored at 2 to 8°C in the commercial container/closure system. The applicant will continue collecting data from the ongoing stability studies.

For future stability testing, the applicant will place (b) (4)

Reference Standards

The primary reference standard is a tested and qualified (b) (4) batch. The purpose of the primary reference standard is to qualify a secondary reference standard lot for routine use as a quantitative standard for relative potency testing of (b) (4) DP lot for release and stability testing. A (b) (4) lot that is assigned as a standard is tested for (b) (4) The reference standard material is stored as (b) (4)

Container Closure System - DP

The primary container for PALFORZIA filled into capsules (0.5 mg, 1.0 mg. 10 mg, 20 mg, and 100 mg doses) are blister strips manufactured using an (b) (4) base material (b) (4) Push Through lidding. The blister strips container closure integrity test method is a (b) (4) that is implemented as (b) (4) in-process check performed by (b) (4) . Representative test results from the blister packaging machine performance qualification studies met acceptance criteria.

The primary container for the PALFORZIA 300 mg dose is the sachet made from a (b) (4) foil-laminate film. (b) (4) foil/(b) (4) layer serves as the contact surface for the drug product. The sachet container closure integrity test is performed in (b) (4) is an in-process (b) (4) Sachet integrity testing data reviewed was acceptable.

b) CBER Lot Release

The lot release protocol templates were submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of oral peanut powder PALFORZIA are listed in Table 8. The activities performed and inspectional histories are also noted in Table 8 and are further described in the paragraphs that follow.

Table 8: Facilities involved in manufacturing, packaging and release testing of PALFORZIA

Name/Address and activities performed	FEI number	DUNS number	Inspection/ Waiver	Justification results
Drug Substance: Disposition of source material as drug substance **Drug Product:** Manufacturing and release testing of drug product **CoreRx, Inc.** 14205 Myerlake Circle, Clearwater, Florida 33760 USA	3007209985	780516717 and 080580013	Pre-license Inspection	CBER/DMPQ June 10-14, 2019 **VAI**
Drug Product: Release testing of drug product (b) (4)	(b) (4)	(b) (4)	Waived	ORA surveillance inspection (b) (4) **NAI**
Drug Product: Release testing of drug product (microbiological limits	(b) (4)	(b) (4)	Waived	ORA surveillance inspection (b) (4) **VAI**

Name/Address and activities performed	FEI number	DUNS number	Inspection/ Waiver	Justification results
and (b) (4) (b) (4)				
Drug Product: Packaging (blister packaging of capsules, secondary packaging, and labeling of blistered capsules and sachets) (b) (4)	(b) (4)	(b) (4)	Waived	ORA surveillance inspection (b) (4) **NAI**
Drug Product: Release testing of drug product (b) (4) testing) (b) (4)	Not Applicable	(b) (4)	Waived	Waiver based on being an established accredited Government Testing Laboratory for (b) (4) testing in foods

CBER conducted a pre-license inspection (PLI) at CoreRx in June 2019 and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

The Office of Regulatory Affairs (ORA) conducted a surveillance inspection of (b) (4) . The inspection was classified as No Action Indicated (NAI).

ORA conducted a surveillance inspection of (b) (4) . All the 483 issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) . (doing business as (b) (4) , contract packager of human and animal drugs, in (b) (4) . The inspection was classified NAI.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

As the active component of PALORZIA is food grade peanut powder, non-clinical studies were not required.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology studies were conducted.

6. CLINICAL/STATISTICAL

a) Clinical Program

Overview of Clinical Studies

The overall clinical development program of PALFORZIA in peanut-allergic children, adolescents, and adults includes two Phase 2 studies (ARC001, ARC002) and five Phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC011). Additionally, a Phase 3 deferred pediatric study (ARC005), is in progress. The study conduct is complete for ARC001, ARC002, ARC003, and ARC007. The two ongoing Phase 3 follow-on safety studies (ARC004, ARC011) were also considered in support of licensure of PALFORZIA in the U.S.

ARC003 was the primary clinical study supportive of safety and efficacy of PALFORZIA. An additional Phase 3 study, ARC007, was also provided as supplemental support for safety. Interim safety data from ARC004 and ARC011 were considered for integrated safety analyses. A summary of clinical trials in the PALFORZIA development program, and more detailed summaries of the studies that contributed to the safety and efficacy data considered in the review (ARC003, ARC004, ARC007, and ARC011), are presented in Table 9 below.

Table 9: Summary of Studies in the PALFORZIA Clinical Program

Study (NCT number)	Phase	Design	Ages (years)	Enrollment	Purpose
ARC001 (Completed) (NCT01987817)	Phase 2	Randomized Double blind Placebo controlled	4-26	56	Safety and Efficacy
ARC002 (Follow on for ARC001) (NCT02198664)	Phase 2	Open label	4-26	47	Additional Safety
ARC003 (Completed) (NCT02635776)	Phase 3	Randomized Double blind Placebo controlled	4-55	555	Safety and Efficacy
ARC004 (Ongoing, Follow on for ARC003) (NCT02993107)	Phase 3	Open label	4-55	388	Safety (daily dose 300 mg)
ARC005 (Ongoing) (NCT03736447)	Phase 3	Randomized Double blind Placebo controlled	1-<4	ongoing	Safety and Efficacy
ARC007 (Completed) (NCT 03126227)	Phase 3	Randomized Double blind Placebo controlled	4-17	506	Safety
ARC008 (Ongoing) (NCT 03292484)	Phase 3	Open label	Follow on	360	Safety (daily dose 300 mg)
ARC011 (Ongoing, Follow on for ARC007) (NCT 03337542)	Phase 3	Open label	4-17	237	Safety (daily dose 300 mg)

Study ARC003 and Follow on Study ARC004

ARC003 was a randomized, double blind, placebo controlled, multicenter Phase 3 study conducted for the evaluation of safety and efficacy of PALFORZIA in peanut allergic subjects ages 4-55 years. Out of 555 total subjects, 496 were 4-17 years of age. The majority of subjects were male (57.3%) and white (78.4%). Black subjects were less than 2% of the total pediatric population enrolled. Subjects with history of asthma, allergy to a food other than peanut, and history of systemic reaction to peanut were equally distributed among both the treatment groups.

Subjects were screened to confirm peanut specific IgE (≥0.35 kUA/L) or skin prick testing to peanut (≥3 mm). Subjects with severe persistent asthma, a history of eosinophilic esophagitis (EoE), those who experienced anaphylaxis within 60 days of

the screening, a history of mast cell disorder, allergy to oat, and hypersensitivity to epinephrine, or other excipients in the product were not enrolled in the study.

Subjects who had dose-limiting symptoms after consuming ≤ 100 mg peanut protein (144 mg cumulative) of food challenge material in a double-blind placebo-controlled food challenge (DBPCFC) at screening were randomized (3:1) to PALFORZIA or placebo. The duration of the treatment was approximately 12 months. The dosing regimen included Initial Dose Escalation of 0.5 mg to 6 mg peanut protein followed by Up-Dosing starting with 3 mg/day reaching up to 300 mg/day with dose escalation every two weeks and finally Maintenance at 300 mg/day daily. Subjects who completed 24 weeks of Maintenance phase were then evaluated in an exit DBPCFC. The primary objective of the study was to demonstrate the reduction in clinical reactivity to limited amounts of peanut allergens.

ARC004 is an ongoing open label Phase 3 follow-on (from ARC003) safety study of daily dosing of PALFORZIA for an extended period of 3 years. Under ARC004 subjects from the PALFORZIA group who tolerated at least 300 mg peanut protein in the exit food challenge continued a daily PALFORZIA dose of 300 mg, and subjects that were enrolled in the placebo-group in ARC003 underwent Initial Dose Escalation and Up-Dosing similar to the procedure used in ARC003. Interim safety data from study ARC004 was included in a pooled safety analysis in the integrated safety population using a safety cutoff date of July 15, 2018. Please see the Safety Section 7 for additional details regarding the pooled safety analysis.

Study ARC007 and Follow on ARC011

ARC007 was a Phase 3 randomized, placebo-controlled safety study conducted in 506 peanut allergic children 4 through 17 years of age to supplement the PALFORZIA safety database. There were no efficacy endpoints in ARC007. Demographics were comparable to the ARC003 population.

Unlike ARC003, the study design for ARC007 did not require that subjects undergo an oral food challenge (OFC) during screening and enrollment. More stringent criteria for physician diagnosed IgE-mediated peanut allergy and serum IgE at screening were used to enroll subjects. Subjects were enrolled and randomized 2:1 to the PALFORZIA (N=338) and placebo (N=168) groups.

Subjects underwent Initial Dose Escalation (0.5 mg to 6 mg) in a single day followed by Up-Dosing from 3 mg to 300 mg/day at two-week intervals. Subjects continued 300 mg/day treatment for two weeks before the study ended. There was no maintenance period and no exit oral food challenge in ARC007. The primary objective of the study was to assess safety and tolerability of PALFORZIA for 6 months. After study exit, the eligible subjects had an option to participate in follow on study ARC011. In ARCC011, subjects will continue taking 300 mg daily maintenance dose for another 6 months. The objective of the study is to collect safety and tolerability data of the 300 mg/day maintenance dose for the duration of the study. At the end of maintenance period, subjects will undergo an exit visit to discuss options for continued treatment based on

a review of current medications, allergen exposures, daily symptom questionnaires, and adverse events.

Summary of PALFORZIA Efficacy

The efficacy of PALFORZIA was established in a single study, ARC003. Efficacy was evaluated in an exit DBPCFC for subjects who were able to complete Maintenance therapy for 24 weeks. Increasing single doses of 3, 10, 30, 100, 300, 600, and 1000 mg peanut protein (2043 mg cumulative) were evaluated in the food challenge. The intent to treat (ITT) population that included all the randomized subjects who received at least one dose of randomized study treatment was used for the primary endpoint analysis. The completer population, which included all subjects in the ITT population who completed treatment and had an evaluable exit DBPCFC, was used for sensitivity and supportive analyses of the primary endpoints.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects who tolerated 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 (i.e., proportion of treatment responders). The pre-specified success criterion for efficacy in the primary analysis was met if the lower bound of the 95% CI of the difference in proportions of responders (PALFORZIA minus placebo) was greater than 15%. All statistical tests were conducted with a two-sided type I error of 0.05. As the number of adult subjects enrolled in ARC003 was limited, the primary efficacy endpoint was revised before unblinding of the trial by amending the subject age from 4 through 55 to 4 through 17 years.

Results from the primary efficacy analysis are shown in Table 10. The primary efficacy success criterion was met. The lower bound of the 95% CI of the difference in proportions of responders (PALFORZIA minus placebo) was 53.0% and exceeded the prespecified success criterion of 15%.

Table 10: Primary Efficacy Endpoint Analyses in the ITT Population in subjects 4 through 17 years of Age in Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (PALFORZIA-Placebo) (95% CI)
PALFORZIA	372	67.2 (62.3, 71.8)	63.2 (53.0, 73.3)
Placebo	124	4.0 (1.7, 9.1)	-

A consistent treatment response was observed in the subgroup analysis for the primary efficacy endpoint as assessed by age groups (4 to 11 years and 12 to 17 years), region (US and Europe), sex (male and female), peanut specific serum IgE (≤100 kUA/L or ≥100 kUA/L), and ethnicity for the ITT population.

Notably, the discontinuation rate due to adverse events and withdrawal of consent was higher in participants 4 through 17 years of age in the PALFORZIA group [N=80 (21.4%)] compared to the placebo group [N=10 (8.0%)]. Efficacy results for the exit DBPCFC were similar as evaluated by conducting sensitivity analyses for missing data. In these analyses, placebo-treated subjects with missing data were considered as responders, PALFORZIA-treated subjects with missing data were considered as non-responders, and subjects with indeterminate DBPCFCs (identified as those without an exit DBPCFC and those who were unable to tolerate at least 1000 mg during the placebo portion of the DBPCFC) were excluded.

Secondary Efficacy Endpoints

The four key secondary efficacy endpoints were tested in hierarchical order as listed below:

1. Desensitization response rate in subjects aged 4 to 17 years at a single dose of 300 mg (443 mg cumulative) of peanut protein at the exit DBPCFC
2. Desensitization response rate in subjects aged 4 to 17 years at a single dose of 1000 mg (2043 mg cumulative) of peanut protein at the exit DBPCFC
3. Maximum severity of symptoms in subjects aged 4 to17 years that occurred at any challenge dose of peanut protein during the exit DBPCFC
4. Desensitization response rate in subjects aged 18 to 55 years at a single dose of 600 mg (1043 mg cumulative) of peanut protein at the exit DBPCFC

The success criteria for desensitization response rates (the first, second, and fourth secondary endpoints) were that the lower bound of the 95% CI of the difference in proportion of responders (PALFORZIA minus placebo) was greater than 0%. The success criterion for the third secondary endpoint was that the p-value of the Cochran-Mantel-Haenszel test for difference in mean severity scores was <0.05.

The success criteria for the first three secondary efficacy endpoints were met for subjects ages 4 through 17 years as indicated in Tables 11 and 12 below. The success criterion for the fourth secondary endpoint, which evaluated the treatment response at a single challenge dose of 600 mg in adult subjects, was not met. The limited number of adult subjects coupled with a high discontinuation rate may have contributed to failure to meet the secondary endpoint.

Table 11: Secondary Efficacy Endpoints Analyses in Subjects 4 through17 years of age: Desensitization to a fixed amount of peanut protein challenge dose

Treatment (N)	Challenge dose	% Responders (95% CI)	% Treatment difference (PALFORZIA-Placebo) (95% CI)
PALFORZIA (372)	300 mg	76.6 (72.1, 80.6)	68.5 (58.6, 78.5)
Placebo (124)	300 mg	8.1(4.4, 14.2)	-

Treatment (N)	Challenge dose	% Responders (95% CI)	% Treatment difference (PALFORZIA-Placebo) (95% CI)
PALFORZIA (372)	1000 mg	50.3 (45.2, 55.3)	47.8 (38.0, 57.7)
Placebo (124)	1000 mg	2.4 (0.8, 6.9)	-

Table 12: Secondary Efficacy Endpoint Analysis of the Maximum Severity of Symptoms at any challenge dose of peanut protein in Subjects 4 through 17 years of age

Treatment (N)	None	Mild	Moderate	Severe
PALFORZIA (372)	140 (37.6%)	119 (32.0%)	94 (25.3%)	19 (5.1%)
Placebo (124)	3 (2.4%)	35 (28.2%)	73 (58.9%)	13 (10.5%)

Overall, the data from ARC003 support the effectiveness of PALFORZIA in mitigating allergic reactions including anaphylaxis during accidental exposure to peanut in patients ages 4 through 17 years.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at six clinical investigator sites that participated in Study ARC003 with four of the sites also participating in Study ARC007. The inspection results did not significantly impact analysis of the data submitted in this BLA.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Aimmune requested a partial waiver of studies of PALFORZIA in children ≤ 1 year of age because studies are impossible or highly impracticable because peanut allergy is not typically diagnosed before the age of 1 year.

Aimmune requested a partial deferral of pediatric studies for ages 1 through < 4 years because this product is ready for approval for use in children 4 through 17 years of age and an ongoing pediatric study in children 1 through < 4 years of age has not been completed.

Aimmune's pediatric study plan was presented to FDA's Pediatric Review Committee on October 1, 2019. The committee agreed with the applicant's request for a partial waiver of studies in children ≤ 1 year of age and a partial deferral of studies in children 1 through < 4 years of age.

The study required by PREA specified in the approval letter for this application, and agreed upon with Aimmune, is the deferred study for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in pediatric patients ages 1 through < 4 years. The applicant will submit the final study report as a supplement to the BLA by June 30, 2022.

7. SAFETY/PHARMACOVIGILANCE

The safety of PALFORZIA was evaluated in clinical studies ARC003, ARC004 (ongoing), ARC007, and ARC011 (ongoing). The results from ARC001 and ARC002 were not considered for the integrated safety assessment due to differences in the study design and data collection.

All subjects who received at least one dose of treatment were used for safety analyses. The controlled safety population included 1001 subjects randomized to treatment with PALFORZIA (N=709) or placebo (N=292). As there were no major differences in the safety assessment methods between ARC007 and ARC003, the controlled safety population included subjects from both of these studies. For the integrated safety analyses, data was pooled from studies ARC003, ARC004, ARC007 and ARC011. The integrated safety population was comprised of 812 subjects treated with PALFORZIA.

Adverse events (AEs), including serious adverse events (SAEs), use of epinephrine as a rescue medication, and frequency of anaphylaxis, were assessed throughout the treatment period. In addition, subjects with gastrointestinal AEs were monitored closely for any symptoms that may indicate development of eosinophilic esophagitis (EoE). Frequency of accidental ingestions and severity of adverse events associated with accidental ingestions of peanut and other allergenic foods were also recorded.

Overall Adverse Events (AEs):

In the controlled and integrated safety populations most of the adverse events were mild to moderate in severity, and the number of AEs in the PALFORZIA group decreased over time from Up-Dosing to Maintenance. The incidence rate of serious adverse events was slightly higher in PALFORZIA recipients compare to placebo recipients in the controlled safety population (overall 1.4% vs. 1.0%, respectively). In the controlled population 98% of subjects in the PALFORZIA group and 95% of subjects in the placebo group reported one or more AEs. Overall, 11.8% subjects in the controlled population and 11.6% of subjects in the integrated population discontinued study treatment due to an AE. Adverse events associated with accidental food allergen exposure were less common in the controlled PALFORZIA group (14%) compared to the placebo group (24.3%). AEs due to accidental food allergen

exposure in the integrated population were 16.9%. The most common treatment-related AEs in the PALFORZIA group were abdominal pain, oral pruritus, and throat irritation.

Deaths:

There were no deaths reported in PALFORZIA recipients. There was one death in the placebo group in study ARC007. This event was a fatal craniocerebral injury related to a motor vehicle accident. The event was not considered related to the study drug.

Non-Fatal Serious Adverse Events (SAEs):

In the controlled safety population, 10 PALFORZIA recipients (6 subjects during Up-Dosing and 4 subjects during Maintenance) and 3 placebo recipients (2 subjects during Up-Dosing and 1 subject during Maintenance) reported SAEs. Three anaphylactic reactions and one asthma exacerbation in the PALFORZIA group were deemed product related. In the integrated safety population, 4 additional subjects experienced SAEs during Maintenance. One systemic allergic reaction was considered related to PALFORZIA. The 3 unrelated SAEs were abdominal pain, dehydration and bacterial infection.

Common Adverse Events (AEs) and discontinuation rates:

The most common AEs in the controlled safety population that were at last 5% higher in the PALFORZIA group compared to placebo in Up-Dosing and Maintenance were predominantly GI complaints (abdominal pain, pruritus, throat irritation, vomiting, nausea). The frequency of the events was similar in both the controlled and integrated safety populations. Compared to Up-Dosing the frequency of these events decreased in the Maintenance phase. Discontinuation rates were also higher during the Up-Dosing phase with 9.7% in the PALFORZIA group compared to 1.4% in the placebo group in the controlled safety population. In the PALFORZIA group, 1.3% of subjects discontinued during Maintenance, mostly due to systemic allergic reaction. The overall discontinuation rate in the integrated safety population was 11.6%, with 9.2% during Up-Dosing. The most common reasons were abdominal pain (3.7%), vomiting (2.5%), nausea (1.7%), and anaphylaxis (1.7%).

Adverse Events of Special Interest (AESI)- Systemic Allergic Reactions Including Anaphylaxis and Epinephrine Use as a Rescue Medication:

In the controlled population, 9.4% of PALFORZIA recipients reported systemic allergic reactions during Initial Dose Escalation and Up-Dosing combined compared to 3.8% of placebo recipients. During maintenance, 8.7% of PALFORZIA recipients and 1.7% of placebo recipients reported systemic allergic reactions. Most systemic allergic reactions in the PALFORZIA group were triggered by study product, and most were mild to moderate in severity. Three subjects in the PALFORZIA group had a serious systemic allergic reaction, with 2 (0.3%) during Up-dosing and 1 (0.3%) during Maintenance phase.

During Initial Dose Escalation and Up-Dosing combined, 6.1% in the PALFORZIA group and 3.1% in the placebo group reported at least 1 episode of epinephrine use. During Maintenance, 7.7% of subjects in the PALFORZIA group and 3.4% of subjects in the placebo group had at least 1 episode of epinephrine use. Epinephrine use as a rescue medication occurred mostly outside of the study site, though a higher proportion occurred at the study site during the Initial Dose Escalation and Up-Dosing compared to Maintenance.

For the integrated safety population, systemic allergic reactions were consistent with the controlled safety population. Most systemic allergic reactions were triggered by the study product. Extrinsic factors such as exercise, exposure to hot water, intercurrent illness and fasting were identified as cofactors contributing to some of the reported systemic allergic reactions. The incidence of systemic allergic reactions appeared to decrease over time during the Maintenance: 32 episodes at 0-13 weeks, 21 episodes at 14-26 weeks, 20 episodes at 27-52 weeks and 6 episodes in subjects who took maintenance dose for over 52 weeks. Severe systemic allergic reactions were reported in 10 subjects (1.2% overall), including no subjects during initial dose escalation, 5 subjects (0.6%) during Up-dosing, and 5 subjects (0.8%) during Maintenance.

Adverse Events of Special Interest (AESI)- Eosinophilic Esophagitis:

In the controlled safety population, 3 (0.4%) PALFORZIA recipients developed biopsy confirmed eosinophilic esophagitis (EoE) during Up-dosing in ARC003. In the integrated safety population, 1 additional subject was diagnosed with EoE during Up-dosing. Another subject diagnosed with biopsy confirmed EoE was reported in the ongoing study ARC004. Five (0.6%) subjects in the integrated safety population had EoE cases by the cutoff date of July 15, 2018. Overall, 12 out of 1050 subjects in the clinical program exposed to PALFORZIA developed EoE (cutoff date of December 21, 2018). No subjects taking placebo were diagnosed with EoE.

Asthma:

Respiratory AEs such as asthma, wheezing, dyspnea, and throat tightness were reported more frequently in subjects with asthma in both PALFORZIA and placebo recipients. PALFORZIA-treated subjects with asthma reported dyspnea and throat tightness more frequently than subjects with asthma in the placebo group. 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%).

Chronic/Recurrent GI AEs:

In the controlled safety population, 55 subjects (7.8%) in the PALFORZIA group and 3 subjects (1.0%) in the placebo group had 1 or more GI related AEs. Of these, 36

subjects in the PALFORZIA group discontinued from the study due to chronic or recurrent GI adverse events.

In the integrated safety population, 62 subjects (7.6%) had 1 or more adverse events in the GI disorders system organ class. Of these, more than half discontinued from the study. For subjects who discontinued, 20 subjects had at least 1 GI adverse event during Initial Dose Escalation, 36 subjects during Up-dosing, and none during Maintenance.

Summary of Safety Findings

No unexpected safety signals were revealed from pooled safety analyses of 4 clinical studies (ARC003, ARC007, ARC004, and ARC011). The safety outcome is consistent among the controlled and integrated population. Safety analysis revealed an increased frequency of systemic allergic reactions, including anaphylaxis, in PALFORZIA recipients compared to placebo recipients (14.2% vs. 3.2% respectively) and a corresponding increase in epinephrine use as a rescue medication (14.0% vs. 6.5%). The discontinuation rate due to AEs, the majority of which were GI symptoms, was higher in PALFORZIA recipients compared to placebo recipients. Cases of EoE are also reported with higher frequency in PALFORZIA treated subjects. The data suggest that PALFORZIA recipients are at higher risk for anaphylaxis, especially associated with the first dose of Up-Dosing levels.

Risk Evaluation and Mitigation Strategies (REMS)

PALFORZIA use in peanut allergic individuals is associated with a risk of systemic allergic reactions to the drug, including anaphylaxis. To ensure that the benefits of PALFORZIA outweigh its risks, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) will be implemented. The elements of the REMS include Prescriber Certification (ETASU A), Dispenser Certification (ETASU B), Dispensing to occur in limited settings (ETASU C), Safe Use Conditions (ETASU D), and Monitoring (ETASU E), as well as an implementation system and timetable for submission of assessments. The goal of the PALFORZIA REMS program is to mitigate the risk of anaphylaxis associated with PALFORZIA, and the following are the objectives of the PALFORZIA REMS program:

1. Healthcare providers who prescribe and healthcare settings that dispense and administer PALFORZIA are certified and educated on:
    - The risk of anaphylaxis associated with the use of PALFORZIA
    - 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. The Initial Dose Escalation and the first dose of each Up-Dosing level of PALFORZIA are only administered to patients in certified healthcare settings.

3. PALFORZIA is only dispensed and administered to patients who are informed, by enrolling in the PALFORZIA REMS Program, of the need to have injectable epinephrine available for immediate use 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 and how to recognize the signs and symptoms of anaphylaxis.

Pharmacovigilance Plan

Aimmune has proposed a routine Pharmacovigilance plan (PVP) for PALFORZIA. Routine PV includes monitoring anaphylaxis and systemic allergic reaction, EoE, concomitant medication that might interfere with epinephrine, and severe asthma. There are multiple ongoing studies to collect additional long-term safety data and to support expansion of the age indication for this product to include individuals 1 to < 4 years old.

- ARC004 and ARC011 are ongoing Phase 3 safety studies for ARC003 and ARC007, respectively.
- ARC008 is a Phase 3 international, open-label, long-term safety study.
- ARC005 is an ongoing Phase 3, international, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of PALFORZIA in peanut-allergic children aged 1 to < 4 years. This study is conducted as a Pediatric Research Equity Act (PREA) postmarketing Requirement (PMR).
- Aimmune will establish a pregnancy registry as a postmarketing Commitment (PMC) to monitor use and safety of PALFORZIA during pregnancy.

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 PMR or PMC safety study other than what is mentioned in Section 11.

8. ADVISORY COMMITTEE MEETING

An Allergenic Products Advisory Committee (APAC) meeting was convened on September 13, 2019, to discuss the safety and efficacy data derived from the studies conducted with PALFORZIA in subjects 4 through 17 years of age. The committee voted (Yes = 7, No = 2) that the available data support the efficacy of PALFORZIA in individuals 4 through 17 years of age. The committee agreed that the available efficacy data are adequate to support the use of PALFORZIA as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis, during accidental exposure to peanut or peanut containing food (as described in Section 10 below, the wording of the approved indication was modified slightly from the proposed indication discussed at the APAC meeting).

The committee also agreed (Yes = 8, No = 1) that the available safety data, in conjunction with additional safeguards (i.e., similar to those ultimately incorporated

into the REMS), are adequate to support the use of PALFORZIA in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

Committee members suggested that the additional safeguards should contain items including informed consent/assent, documentation that patients and caregivers continue to maintain a peanut-avoidant diet, and guidance on missed doses. The concerns raised during the meeting were considered during the generation of the Prescribing Information, Medication Guide, and REMS document.

9. OTHER RELEVANT REGULATORY ISSUES

None

10. LABELING

The proposed proprietary name, PALFORZIA, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) and found to be acceptable on May 21, 2019. CBER communicated the acceptability of the proprietary name to the applicant on June 05, 2019.

APLB reviewed the proposed prescribing information (PI), patient labeling, and package/container from a comprehension and promotional perspective and provided comments to the review committee in a memorandum dated December 09, 2019.

The Review Committee negotiated revisions to the PI, including: the proposed proper name, the indication, the boxed warning, the dosage and administration section, the warnings and precautions, and reporting of adverse events. The proper name was revised to include the term "Powder" as a part of the proper name. This is because the final DP is administered by opening the capsules or sachets and mixing the powder in a food medium for oral consumption. Thus, the review team recommended that the term "Powder" is necessary to be a part of the proper name in addition to the dosage form. Aimmune proposed the indication: "PALFORZIA is indicated as an oral immunotherapy treatment 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." The indication was subsequently revised to "PALFORZIA is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. PALFORZIA is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up-Dosing and Maintenance may be continued in patients 4 years of age and older".

A limitation of use, "Not indicated for the emergency treatment of allergic reactions, including anaphylaxis," was added to the Indication and Usage section.

The boxed warning was revised by adding wording regarding an observation period after the Initial Dose Escalation and after each dose during in-clinic Up Dosing and noting the restricted availability of PALFORZIA through a REMS program.

The Warnings and Precautions section was revised for additional clarity in describing signs and symptoms of allergic reactions and other conditions such as anaphylaxis, asthma, eosinophilic esophagitis, and gastrointestinal reactions. An overview of the REMS program was added under Section 5, “Warnings and Precautions.”

The review committee also provided revisions to the medication guide to ensure consistency with the PI and the REMS program.

All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical and product-related data submitted in this BLA, the Review Committee recommends approval of PALFORZIA for the labeled indication and usage.

b) Risk/ Benefit Assessment

Peanut allergy is a serious condition, and there is an unmet medical need for peanut allergy treatment in patients aged 4 through 17 years. A review of the efficacy data submitted by the applicant demonstrates that PALFORZIA mitigates the severity of allergic symptoms when subjects are exposed to controlled amounts of peanut protein during oral food challenge, which is accepted as a surrogate for mitigation of allergic reactions following accidental peanut exposure.

PALFORZIA presents safety risks, such as anaphylaxis, EoE, and other adverse reactions characterized mainly by GI symptoms. Thus, the review committee requires implementation of a risk evaluation and mitigation strategy (REMS) program to assure that the benefits of PALFORZIA outweigh the risk of anaphylaxis. The program will ensure that patients have injectable epinephrine available for use at all times, continue to avoid peanut in the diet, and are observed in a clinical setting capable to treat systemic allergic reactions when patients undergo Initial Dose Escalation or are administered the first dose of a dose increase during Up-Dosing. Patients will be counseled about the risks of systemic allergic reactions and will be directed to contact a health care professional if any of these signs or symptoms occur.

Despite the risk of anaphylaxis caused by PALFORZIA, the conditions of the REMS program will ensure that this risk is manageable, and the overall risks of PALFORZIA in association with the REMS program are offset by its clear benefit in mitigating allergic reactions following accidental peanut exposure. The risk/benefit balance of PALFORZIA in association with its REMS program is therefore favorable and supports

approval for use as an oral immunotherapy for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

c) Recommendation for Postmarketing Activities

Aimmune has committed to conduct the following Postmarketing activities, which are specified in the PALFORZIA approval letter:

1. **Pediatric Requirement**

   Deferred pediatric study under PREA for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in pediatric patients ages 1 through < 4 years.

   Protocol Submission under IND 15463: October 4, 2018
   Study Completion: December 31, 2021
   Final Report Submission: June 30, 2022

2. **Pregnancy Registry**

   PALFORZIA pregnancy registry as a Postmarketing Commitment (PMC) to monitor use and safety of PALFORZIA during pregnancy.

   Protocol Submission: February 28, 2020
   Study Completion: January 1, 2025
   Final Report Submission: January 30, 2026

12. REFERENCES

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