HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PALFORZIA safely and effectively. See Full Prescribing Information for PALFORZIA.

PALFORZIA [Peanut (*Arachis hypogaea*) Allergen Powder-dnfp]
Powder for oral administration

Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Boxed Warning	7/2024
Indications and Usage (1)	7/2024
Dosage and Administration, Dosage (2.2)	7/2024
Dosage and Administration, Administration (2.4)	7/2024
Dosage and Administration, Schedule Modification and Product Discontinuation (2.5)	7/2024
Warnings and Precautions, Anaphylaxis (5.1)	7/2024
Warnings and Precautions, Eosinophilic Gastrointestinal Disease (5.4)	7/2024
Warnings and Precautions, Gastrointestinal Adverse Events (5.5)	7/2024

WARNING: ANAPHYLAXIS

See Full Prescribing Information for complete boxed warning.

- **PALFORZIA can cause anaphylaxis (also called anaphylactic reaction), which may be life-threatening and can occur at any time during PALFORZIA therapy (5.1).**
- **Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use (5.1).**
- **Do not administer PALFORZIA to patients with uncontrolled asthma (4).**
- **Dose modifications may be necessary following an anaphylactic reaction (2.5).**
- **Observe patients during and after administration of the Initial Dose Escalation and the first dose of each new Up-Dosing level, for at least 60 minutes (2.4).**
- **PALFORZIA is available only through a restricted program called the PALFORZIA REMS (5.2).**

----------INDICATIONS AND USAGE----------

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 1 through 17 years. Up-Dosing and Maintenance may be continued in patients 1 year of age and older (2.4).

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.

----------DOSAGE AND ADMINISTRATION----------

For oral administration only (2)

- Do not swallow capsule(s).
- Do not inhale powder.
- Open capsule(s) or sachet and empty the entire dose of PALFORZIA powder onto refrigerated or room temperature semisolid food.
- Mix well.
- Consume the entire volume.

Initial Dose Escalation – Ages 1 through 3 years

Total Dose	Dose Configuration
0.5 mg	One 0.5 mg capsule
1 mg	One 1 mg capsule
1.5 mg	One 0.5 mg capsule; One 1 mg capsule
3 mg	Three 1 mg capsules

Initial Dose Escalation – Ages 4 through 17 years

Total Dose	Dose Configuration
0.5 mg	One 0.5 mg capsule
1 mg	One 1 mg capsule
1.5 mg	One 0.5 mg capsule; One 1 mg capsule
3 mg	Three 1 mg capsules
6 mg	Six 1 mg capsules

Up-Dosing

Total Daily Dose	Daily Dose Configuration	Patient Age (years)
1 mg	One 1 mg capsule	1-3
3 mg	Three 1 mg capsules	1-17
6 mg	Six 1 mg capsules	1-17
12 mg	Two 1 mg capsules; One 10 mg capsule	1-17
20 mg	One 20 mg capsule	1-17
40 mg	Two 20 mg capsules	1-17
80 mg	Four 20 mg capsules	1-17
120 mg	One 20 mg capsule; One 100 mg capsule	1-17
160 mg	Three 20 mg capsules; One 100 mg capsule	1-17
200 mg	Two 100 mg capsules	1-17
240 mg	Two 20 mg capsules; Two 100 mg capsules	1-17
300 mg	One 300 mg sachet	1-17

Maintenance

Total Daily Dose	Daily Dose Configuration
300 mg	One 300 mg sachet

----------DOSAGE FORMS AND STRENGTHS----------

Powder for oral administration supplied in 0.5 mg, 1 mg, 10 mg, 20 mg and 100 mg Capsules or 300 mg Sachets.

----------CONTRAINDICATIONS----------

- Uncontrolled asthma (5.3).
- History of eosinophilic esophagitis, or other eosinophilic gastrointestinal disease (5.4 and 5.5).

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis: PALFORZIA can cause anaphylaxis. Educate patients to recognize the signs and symptoms of anaphylaxis. Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use (5.1).
- Asthma: Ensure patients with asthma have their asthma under control prior to initiation of PALFORZIA. PALFORZIA should be temporarily withheld if the patient is experiencing an acute asthma exacerbation. PALFORZIA has not been studied in patients with severe asthma (5.3).
- Eosinophilic esophagitis: PALFORZIA is associated with eosinophilic esophagitis. Monitor patients for signs and symptoms and discontinue PALFORZIA if eosinophilic esophagitis is suspected (5.4).
- Gastrointestinal reactions: If patients develop chronic or recurrent local gastrointestinal allergic symptoms, consider dose modification or discontinuation of treatment (5.5).

----------ADVERSE REACTIONS----------

The most common adverse reactions reported in subjects ages 1 through 3 years treated with PALFORZIA (incidence ≥ 5%) are:

Cough, sneezing, rhinitis, nasal congestion, throat irritation, wheezing, abdominal pain, vomiting, diarrhea, oral pruritus, oropharyngeal pain, urticaria, rash, pruritis, perioral dermatitis.

The most common adverse reactions reported in subjects ages 4 through 17 years treated with PALFORZIA (incidence ≥ 5% and at least 5 percentage points greater than that reported in subjects treated with placebo) are:

Abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylactic reaction, and ear pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics at toll-free phone 1-833-246-2566 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2024

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FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

- **PALFORZIA can cause anaphylaxis (also called anaphylactic reaction), which may be life-threatening and can occur at any time during PALFORZIA therapy *[see Warnings and Precautions (5.1)]*.**
- **Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use *[see Warnings and Precautions (5.1)]*.**
- **Do not administer PALFORZIA to patients with uncontrolled asthma *[see Contraindications (4)]*.**
- **Dose modifications may be necessary following an anaphylactic reaction *[see Dosage and Administration (2.5)]*.**
- **Observe patients during and after administration of the Initial Dose Escalation and the first dose of each new Up-Dosing level, for at least 60 minutes *[see Dosage and Administration (2.4)]*.**
- **Because of the risk of anaphylaxis, PALFORZIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALFORZIA REMS *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

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 1 through 17 years. Up-Dosing and Maintenance may be continued in patients 1 year of age and older *[see Dosage and Administration (2.4)]*.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Considerations Prior to Initiation and During Therapy

Verify that the patient has injectable epinephrine and instruct patient on its appropriate use *[see Warnings and Precautions (5.2)]*.

2.2 Dosage

Treatment with PALFORZIA is administered in 3 sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance.

The dose configurations for each phase of dosing are provided in Table 1 through Table 4.

Table 1: Dosing Configuration for Initial Dose Escalation Ages 1 through 3 years (Single Day Dose Escalation)

Dose Level	Total Dose	Dose Configuration
A	0.5 mg	One 0.5 mg capsule
B	1 mg	One 1 mg capsule
C	1.5 mg	One 0.5 mg capsule; One 1 mg capsule
D	3 mg	Three 1 mg capsules

Initial Dose Escalation supplied as a single card consisting of 4 blisters containing a total of 7 capsules.

Table 2: Dosing Configuration for Initial Dose Escalation Ages 4 through 17 years (Single Day Dose Escalation)

Dose Level	Total Dose	Dose Configuration
A	0.5 mg	One 0.5 mg capsule
B	1 mg	One 1 mg capsule
C	1.5 mg	One 0.5 mg capsule; One 1 mg capsule
D	3 mg	Three 1 mg capsules
E	6 mg	Six 1 mg capsules

Initial Dose Escalation supplied as a single card consisting of 5 blisters containing a total of 13 capsules.

Table 3: Daily Dosing Configuration for Up-Dosing

Dose Level	Total Daily Dose	Daily Dose Configuration	Dose Duration (weeks)	Patient age (years)
0	1 mg	One 1 mg capsule	2	1 - 3
1	3 mg	Three 1 mg capsules	2	1 – 17
2	6 mg	Six 1 mg capsules	2	1 – 17
3	12 mg	Two 1 mg capsules; One 10 mg capsule	2	1 – 17
4	20 mg	One 20 mg capsule	2	1 – 17
5	40 mg	Two 20 mg capsules	2	1 – 17
6	80 mg	Four 20 mg capsules	2	1 – 17
7	120 mg	One 20 mg capsule; One 100 mg capsule	2	1 – 17
8	160 mg	Three 20 mg capsules; One 100 mg capsule	2	1 – 17
9	200 mg	Two 100 mg capsules	2	1 – 17
10	240 mg	Two 20 mg capsules; Two 100 mg capsules	2	1 – 17
11	300 mg	One 300 mg sachet	2	1 – 17

Table 4: Daily Dosing Configuration for Maintenance

Dose Level	Total Daily Dose	Daily Dose Configuration
11	300 mg	One 300 mg sachet

2.3 Preparation and Handling

PALFORZIA is to be administered orally.

- Open capsule(s) or sachet and empty the entire dose of PALFORZIA powder onto a few spoonfuls of refrigerated or room temperature semisolid food (e.g., applesauce, yogurt, pudding). Do not use liquid (e.g., milk, water, juice) to prepare.
- Mix well.
- Consume the entire volume of the prepared mixture promptly.
- Dispose of the opened capsule(s) or sachet.
- Wash hands immediately after handling PALFORZIA capsule(s) or sachets.
- Dispose of all unused PALFORZIA.

2.4 Administration

- For oral administration only.
- Do not swallow capsule(s).
- Do not inhale powder.

Initial Dose Escalation

Initial Dose Escalation is administered on a single day under the supervision of a health care professional in a health care setting with the ability to manage potentially severe allergic reactions, including anaphylaxis.

Initial Dose Escalation is administered in sequential order on a single day beginning at Level A; Table 1 (patients 1 through 3 years of age) and Table 2 (patients 4 through 17 years of age).

- Patients 1 through 3 years of age: Levels A through D, 0.5 - 3 mg (4 doses total)
- Patients 4 through 17 years of age: Levels A through E, 0.5 - 6 mg (5 doses total)

Each dose should be separated by an observation period of 20 to 30 minutes.

No dose level should be omitted.

Observe patients after the last dose for at least 60 minutes until suitable for discharge.

Discontinue PALFORZIA if symptoms requiring medical intervention (e.g., use of epinephrine) occur with any dose during Initial Dose Escalation *[see Dosage and Administration (2.5)]*.

Patients 1 through 3 years of age who tolerate all doses (Level A – D) of PALFORZIA during Initial Dose Escalation must return to the health care setting for initiation of Up-Dosing.

Patients 4 through 17 years of age who tolerate at least the 3 mg single dose (Level D) of PALFORZIA during Initial Dose Escalation must return to the health care setting for initiation of Up-Dosing.

If possible, begin Up-Dosing the day after Initial Dose Escalation.

Repeat Initial Dose Escalation in a health care setting if the patient is unable to begin Up-Dosing within 4 days.

Up-Dosing

Complete Initial Dose Escalation before starting Up-Dosing.

Patients 1 through 3 years of age: Up-Dosing consists of 12 dose levels and is initiated at a 1 mg dose (Level 0) and up-dosed to Level 11.

Patients 4 through 17 years of age: Up-Dosing consists of 11 dose levels and is initiated at a 3 mg dose (Level 1) and up-dosed to Level 11.

The first dose of each new Up-Dosing level is administered under the supervision of a health care professional in a health care setting with the ability to manage potentially severe allergic reactions, including anaphylaxis.

Observe patients after administering the first dose of a new Up-Dosing level for at least 60 minutes until suitable for discharge.

If the patient tolerates the first dose of a new Up-Dosing level, the patient may continue that dose level at home. Each dose should be consumed daily with a meal at approximately the same time each day, preferably in the evening.

Administer all the dose levels in Table 3 in sequential order at 2-week intervals, if tolerated.

No dose level should be omitted.

Do not progress through Up-Dosing more rapidly than shown in Table 3.

No more than 1 dose should be consumed per day. Instruct patients not to consume a dose at home on the same day as a dose consumed in the clinic.

Consider dose modification or discontinuation for patients who do not tolerate Up-Dosing as described in Table 3 *[see Dosage and Administration (2.5)]*.

Maintenance

Complete all dose levels of Up-Dosing before starting Maintenance.

The Maintenance dose of PALFORZIA is 300 mg daily.

Daily Maintenance is required to maintain the effect of PALFORZIA.

During Maintenance, contact patient at regular intervals to assess for adverse reactions to PALFORZIA.

2.5 Schedule Modification and Product Discontinuation

Dose Modification

Dose modifications are not appropriate during Initial Dose Escalation.

Temporary dose modification of PALFORZIA may be required for patients who experience allergic reactions during Up-Dosing or Maintenance, for patients who miss doses, or for practical reasons of patient management. Allergic reactions, including gastrointestinal reactions, that are severe, recurrent, bothersome, or last longer than 90 minutes during Up-Dosing or Maintenance should be actively managed with dose modifications. Use clinical judgment to determine the best course of action, which can include maintaining the dose level for longer than 2 weeks, reducing, withholding, or discontinuing PALFORZIA doses.

Management of Consecutive Missed Doses

Following 1 to 2 consecutive days of missed doses, patients may resume PALFORZIA at the same dose level. Data are insufficient to inform resumption of PALFORZIA following 3 or more consecutive days of missed doses. Patients who miss 3 or more consecutive days of PALFORZIA should consult their healthcare providers; resumption of PALFORZIA should be done under medical supervision.

Discontinuation of PALFORZIA

Discontinue treatment with PALFORZIA for:

- Patients 1 through 3 years of age who are unable to tolerate any dose during the Initial Dose Escalation
- Patients 4 through 17 years of age who are unable to tolerate doses up to and including the 3 mg dose during the Initial Dose Escalation
- Patients with suspected eosinophilic esophagitis *[see Warnings and Precautions (5.4 and 5.5)]*
- Patients unable to comply with the daily dosing requirements
- Patients with recurrent asthma exacerbations or persistent loss of asthma control

3 DOSAGE FORMS AND STRENGTHS

PALFORZIA powder description and dosage strengths are as follows:

- 0.5 mg: white to off-white fine granular oral powder (may contain clumps) in white opaque capsules with Aimmune printed on the body and 0.5 mg printed on the cap in grey ink
- 1 mg: white to off-white fine granular oral powder (may contain clumps) in red opaque capsules with Aimmune printed on the body and 1 mg printed on the cap in white ink
- 10 mg: white to off-white fine granular oral powder (may contain clumps) in blue opaque capsules with Aimmune printed on the body and 10 mg printed on the cap in white ink
- 20 mg: off-white to light beige fine granular oral powder (may contain clumps) in white opaque capsules with Aimmune printed on the body and 20 mg printed on the cap in grey ink
- 100 mg: beige fine oral powder (may contain clumps) in red opaque capsules with Aimmune printed on the body and 100 mg printed on the cap in white ink
- 300 mg: beige fine oral powder (may contain clumps) in white foil-laminate sachets with printed information

Combinations of capsules for doses are described in *Dosage and Administration (2.2)*.

4 CONTRAINDICATIONS

PALFORZIA is contraindicated in patients with the following:

- Uncontrolled asthma *[see Warnings and Precautions (5.3)]*
- History of eosinophilic esophagitis and other eosinophilic gastrointestinal disease *[see Warnings and Precautions (5.4 and 5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

PALFORZIA can cause anaphylaxis, which may be life-threatening.

Anaphylaxis has been reported during all phases of PALFORZIA dosing, including Maintenance and in subjects who have undergone recommended Up-Dosing and dose modification procedures.

In 709 PALFORZIA-treated subjects and 292 placebo-treated subjects, ages 4 through 17, in the placebo-controlled population in Studies 1 and 2 combined *[see Adverse Reactions (6.1)]*, anaphylaxis was reported in 9.4% of PALFORZIA-treated subjects compared with 3.8% of placebo-treated subjects during Initial Dose Escalation and Up-Dosing combined, and in 8.7% of PALFORZIA-treated subjects compared with 1.7% of placebo--treated subjects during Maintenance in Study 1. Epinephrine use for any reason was reported in 10.4% of PALFORZIA-treated subjects compared with 4.8% of placebo-treated subjects during Initial Dose Escalation and Up-Dosing combined, and in 7.7% of PALFORZIA-treated subjects compared with 3.4% of placebo-treated subjects during Maintenance dosing in Study 1. Among events of anaphylaxis in PALFORZIA-treated subjects, time to onset after dosing was as follows: within 2 hours (70%), greater than 2 hours and up to 10 hours (18%), or greater than 10 hours (12%). For anaphylactic reactions with time to onset after dosing within 2 hours 98.6%, greater than 2 hours and up to 10 hours 73.7%, and greater than 10 hours 53.8% of events were related to PALFORZIA.

In 98 PALFORZIA-treated subjects and 48 placebo-treated subjects ages 1 through 3 in the placebo-controlled population in Study 3 *[see Adverse Reactions (6.1)]*, anaphylaxis was reported in 8.2% of PALFORZIA-treated subjects (0% during Initial Dose Escalation, 2.0% during Up-Dosing, and 6.9% during Maintenance) compared with 8.3% of placebo-treated subjects. Out of the 9 total anaphylaxis events in PALFORZIA-treated subjects, 3 were related to study drug. There were no reported uses of epinephrine in PALFORZIA-treated or placebo-treated subjects during Initial Dose Escalation. Epinephrine use for any reason was reported in 6.1% of PALFORZIA-treated subjects compared with 2.1% of placebo-treated subjects during Up-Dosing, and in 5.7% of PALFORZIA-treated subjects compared with 4.4% of placebo-treated subjects during Maintenance dosing in Study 3. Among events of anaphylaxis in PALFORZIA-treated subjects, time to onset after dosing was as follows: within 2 hours (33.3%) and greater than 10 hours (66.7%). For anaphylactic reactions with time to onset after dosing within 2 hours 66.7% and reactions with time to onset greater than 10 hours 16.7% of events were related to PALFORZIA.

PALFORZIA may not be suitable for patients who have a history of severe or life-threatening anaphylaxis to peanut, especially patients with severe or life-threatening reactions that have occurred recently since these patients may be at increased risk of anaphylaxis from PALFORZIA. PALFORZIA may not be suitable for patients with certain medical conditions that may reduce the ability to survive anaphylaxis, including but not limited to markedly compromised lung function, severe mast cell disorder, or cardiovascular disease. In addition, PALFORZIA may not be suitable for patients taking medications that can inhibit or potentiate the effects of epinephrine.

All Initial Dose Escalation doses and the first dose of each new Up-Dosing level must be administered under observation in a health care setting *[see Dosage and Administration (2.5)]*. Prior to initiating PALFORZIA treatment, educate patients to recognize the signs and symptoms of anaphylaxis. Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. Instruct patients to contact their health care professional before administering the next dose of PALFORZIA if anaphylaxis or symptoms of an

escalating or persistent allergic reaction occur as dose modification may be necessary *[see Dosage and Administration (2.4)]*.

Patients may be more likely to experience allergic reactions following PALFORZIA administration in the presence of cofactors such as exercise, hot water exposure, intercurrent illness (e.g., viral infection), or fasting. Other potential cofactors may include menstruation, sleep deprivation, nonsteroidal anti-inflammatory drug use, or uncontrolled asthma. Patients should be proactively counseled about the potential for the increased risk of anaphylaxis in the presence of these cofactors. If possible, adjust the time of dosing to avoid these cofactors. If it is not possible to avoid these cofactors, consider withholding PALFORZIA temporarily.

If appropriate to re-start administering PALFORZIA in patients who experienced anaphylaxis while on PALFORZIA or who had doses withheld to avoid increased risk of anaphylaxis, consider a dose reduction and dose re-escalation based on clinical judgment *[see Dosage and Administration (2.5)]*.

PALFORZIA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 PALFORZIA REMS Program

PALFORZIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALFORZIA REMS because of the risk of anaphylaxis *[see Warnings and Precautions (5.1)]*.

Notable requirements of the PALFORZIA REMS include the following:

- Health care providers who prescribe PALFORZIA must be certified with the program by enrolling.
- Health care settings must be certified in the program, have on-site access to equipment and personnel trained to manage anaphylaxis, and establish policies and procedures to verify that patients are monitored during and after the Initial Dose Escalation and first dose of each new Up-Dosing level.
- Patients must be enrolled in the program prior to initiation of PALFORZIA treatment and must be informed of the need to have injectable epinephrine available for immediate use at all times, the need for monitoring with the Initial Dose Escalation and first dose of each new Up-Dosing level, the need for continued dietary peanut avoidance, and how to recognize the signs and symptoms of anaphylaxis.
- Pharmacies must be certified with the program and must only dispense PALFORZIA to health care settings that are certified or to patients who are enrolled depending on the treatment phase.

Further information, including a list of certified prescribers, health care settings, and pharmacies, is available at www.PALFORZIAREMS.com or 1-844-PALFORZ (1-844-725-3679).

5.3 Asthma

Uncontrolled asthma is a risk factor for a serious outcome, including death, in anaphylaxis. Ensure patients with asthma have their asthma under control prior to initiation of PALFORZIA.

PALFORZIA should be temporarily withheld if the patient is experiencing an acute asthma exacerbation. Following resolution of the exacerbation, resumption of PALFORZIA should be

undertaken cautiously *[see Dosage and Administration (2.5)]*. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of PALFORZIA. PALFORZIA has not been studied in subjects with severe asthma, persistently uncontrolled asthma, or patients on long-term systemic corticosteroid therapy.

5.4 Eosinophilic Gastrointestinal Disease

In clinical studies 1 and 2, 28 of 1050 (2.7%) subjects were referred for a gastroenterology evaluation and 17 of these 28 subjects reported undergoing an esophagogastroduodenoscopy (EGD). Of subjects who underwent an EGD, 12 were diagnosed with biopsy-confirmed eosinophilic esophagitis while receiving PALFORZIA compared with 0 of 292 (0%) subjects receiving placebo. After discontinuation of PALFORZIA, symptomatic improvement was reported in 12 of 12 subjects. In 8 subjects with available follow-up biopsy results, eosinophilic esophagitis was resolved in 6 subjects and improved in 2 subjects *[see Contraindications (4)]*.

In Study 3 there were no subjects ages 1 through 3 diagnosed with eosinophilic esophagitis. No subject with chronic or recurrent gastrointestinal event was diagnosed with eosinophilic esophagitis. No subjects were seen by a GI specialist, no biopsies were done.

Discontinue PALFORZIA and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, vomiting, nausea, gastroesophageal reflux, chest pain, or abdominal pain *[see Warnings and Precautions (5.5)]*.

5.5 Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions, including abdominal pain, vomiting, nausea, oral pruritus, and oral paresthesia, were commonly reported in PALFORZIA-treated subjects in the placebo-controlled clinical study population *[see Adverse Reactions (6,* Table 5 and Table 6*)]*. Dose modification should be considered for patients who report these reactions *[see Dosage and Administration (2.5)].* Consider discontinuing PALFORZIA in patients who continue to have chronic or recurrent gastrointestinal symptoms.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Use of PALFORZIA has been associated with:

- Anaphylaxis *[see Warnings and Precautions (5.1)]*
- Eosinophilic esophagitis *[see Warnings and Precautions (5.4)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with the adverse reaction rates in clinical trials of another drug and may not reflect the rates observed in practice.

The clinical data for PALFORZIA reflect exposure in 807 peanut-allergic subjects aged 1 through 17 years enrolled in three phase 3, double-blind, placebo-controlled trials (Study 1, Study 2, and Study 3), and in long-term, open-label, follow-on studies. In Study 1, subjects were Up-Dosed for 20-40 weeks, followed by Maintenance dosing for 24-28 weeks. In Study 2 subjects were Up-Dosed for 20-40 weeks up to a 300 mg daily dose with no extended Maintenance dosing. In Study 3, subjects were Up-Dosed for approximately 6 months (maximum 40 weeks) followed by Maintenance

dosing for 12-24 weeks. In these studies, subjects recorded adverse reactions daily in an electronic diary card throughout the study duration.

Study 1 (NCT02635776) was a randomized, double-blind, placebo-controlled efficacy and safety study conducted in the United States, Canada, and Europe evaluating PALFORZIA versus placebo in 555 subjects aged 4 through 55 years with peanut allergy. Subjects were required to have serum IgE to peanut ≥ 0.35 kUA/L within 12 months before study entry and/or a mean wheal diameter on skin prick test to peanut ≥ 3 mm greater than the negative control. The primary analysis population was aged 4 through 17 years, 78% white and 57% male. At study entry, subjects reacted at 100 mg or less of peanut protein in a double-blind, placebo-controlled food challenge (DBPCFC). The primary analysis was conducted in 496 subjects aged 4 through 17 years (PALFORZIA, N = 372; placebo, N = 124). Of the subjects aged 4 through 17 years treated with PALFORZIA, 72% had a medical history of anaphylactic reactions to peanut, 66% reported multiple food allergies, 63% had a medical history of atopic dermatitis, and 53% had a present or previous diagnosis of asthma. Subjects with severe persistent or uncontrolled asthma were excluded.

Study 2 (NCT03126227) was a randomized, double-blind, placebo-controlled safety study conducted in the United States and Canada evaluating PALFORZIA versus placebo in 506 subjects aged 4 through 17 years with peanut allergy. Subjects were required to have a clinical history of peanut allergy including onset of characteristic allergic signs and symptoms within 2 hours of known oral exposure to peanut, serum IgE to peanut of ≥ 14 kUA/L and a mean wheal diameter on skin prick test ≥ 8 mm greater than the negative control at screening. Subjects were not required to complete a DBPCFC for study entry. The study duration was approximately 6 months and compared the safety and tolerability of PALFORZIA (N = 337) with placebo (N = 168). Most subjects were male (63%) and white (79%). Of the subjects treated with PALFORZIA, 60.5% had a medical history of anaphylactic reactions, 65.0% reported multiple food allergies, 57.9% had a medical history of atopic dermatitis, and 52.2% had a present or previous diagnosis of asthma. Subjects with severe persistent or uncontrolled asthma were excluded.

Across these two phase 3, double-blind, placebo-controlled, randomized clinical studies the most common adverse reactions in subjects treated with PALFORZIA (incidence ≥ 5% and at least 5 percentage points greater than in subjects treated with placebo) were gastrointestinal, respiratory, and skin symptoms commonly associated with allergic reactions, as shown in Table 5.

Table 5: Treatment-Emergent Adverse Reactions in ≥ 5% of PALFORZIA-Treated Subjects and ≥ 5% Percentage Points Greater Than Placebo-Treated Subjects in any Dosing Phase (Aged 4 through 17 Years)

System Organ Class / Preferred Term [2]	Study 1 & Study 2 IDE PALFORZIA (N = 709)	Study 1 & Study 2 IDE Placebo (N = 292)	Study 1 & Study 2 Up-Dosing PALFORZIA (N = 693)	Study 1 & Study 2 Up-Dosing Placebo (N = 289)	Study 1 [1] 300 mg PALFORZIA (N = 310)	Study 1 [1] 300 mg Placebo (N = 118)
Gastrointestinal disorders						
Abdominal pain [3]	185 (26.1%)	24 (8.2%)	465 (67.1%)	100 (34.6%)	90 (29.0%)	20 (16.9%)
Vomiting	22 (3.1%)	2 (0.7%)	253 (36.5%)	47 (16.3%)	50 (16.1%)	14 (11.9%)
Nausea	60 (8.5%)	2 (0.7%)	224 (32.3%)	41 (14.2%)	45 (14.5%)	8 (6.8%)
Oral pruritus [4]	62 (8.7%)	9 (3.1%)	216 (31.2%)	30 (10.4%)	51 (16.5%)	7 (5.9%)
Oral paresthesia	13 (1.8%)	7 (2.4%)	94 (13.6%)	11 (3.8%)	23 (7.4%)	2 (1.7%)
Respiratory, thoracic, and mediastinal disorders						
Throat irritation	66 (9.3%)	15 (5.1%)	279 (40.3%)	49 (17.0%)	43 (13.9%)	11 (9.3%)
Cough	18 (2.5%)	1 (0.3%)	221 (31.9%)	68 (23.5%)	61 (19.7%)	22 (18.6%)
Rhinorrhea	9 (1.3%)	4 (1.4%)	145 (20.9%)	50 (17.3%)	46 (14.8%)	9 (7.6%)
Sneezing	24 (3.4%)	8 (2.7%)	140 (20.2%)	31 (10.7%)	33 (10.6%)	5 (4.2%)

System Organ Class / Preferred Term [2]	Study 1 & Study 2 IDE PALFORZIA (N = 709)	Study 1 & Study 2 IDE Placebo (N = 292)	Study 1 & Study 2 Up-Dosing PALFORZIA (N = 693)	Study 1 & Study 2 Up-Dosing Placebo (N = 289)	Study 1 [1] 300 mg PALFORZIA (N = 310)	Study 1 [1] 300 mg Placebo (N = 118)
Throat tightness	18 (2.5%)	3 (1.0%)	98 (14.1%)	8 (2.8%)	20 (6.5%)	0 (0.0%)
Wheezing	4 (0.6%)	0 (0.0%)	85 (12.3%)	21 (7.3%)	19 (6.1%)	10 (8.5%)
Dyspnea	2 (0.3%)	1 (0.3%)	53 (7.6%)	5 (1.7%)	17 (5.5%)	1 (0.8%)
Skin and subcutaneous tissue disorders						
Pruritus	56 (7.9%)	16 (5.5%)	225 (32.5%)	59 (20.4%)	45 (14.5%)	14 (11.9%)
Urticaria	28 (3.9%)	10 (3.4%)	197 (28.4%)	54 (18.7%)	63 (20.3%)	17 (14.4%)
Immune system disorders						
Anaphylactic reaction [5]	5 (0.7%)	1 (0.3%)	63 (9.1%)	10 (3.5%)	27 (8.7%)	2 (1.7%)
Ear and labyrinth disorders						
Ear pruritus	5 (0.7%)	1 (0.3%)	41 (5.9%)	2 (0.7%)	7 (2.3%)	0 (0.0%)

At each level of summarization (any event, system organ class, or preferred term) subjects with more than 1 adverse reaction were counted only once within each study period.

[1] In Study 2, no adverse reactions ≥ 5% were reported in subjects following treatment with 300 mg PALFORZIA (N = 265).

[2] Adverse events were coded to system organ class and preferred term using the MedDRA, version 19.1.

[3] Includes preferred terms of abdominal pain, abdominal pain upper, and abdominal discomfort.

[4] Includes preferred terms of oral pruritus, tongue pruritis, and lip pruritus.

[5] The anaphylactic reaction preferred term includes systemic allergic reactions of any severity, of which severe anaphylaxis was reported in 4 PALFORZIA-treated subjects (0.6%) during Up-Dosing and 1 PALFORZIA-treated subject (0.3%) during Maintenance.

IDE, Initial Dose Escalation; MedDRA, Medical Dictionary for Regulatory Activities.

A total of 155 (21.9%) PALFORZIA-treated subjects and 19 (6.5%) placebo-treated subjects discontinued for any reason in Studies 1 and 2. Adverse reactions led to study discontinuation in 9.2% PALFORZIA--treated subjects and 1.7% placebo-treated subjects during Initial Dose Escalation and Up-Dosing combined in Studies 1 and 2, and 1.0% PALFORZIA-treated subjects and no placebo-treated subjects during Maintenance dosing in Study 1. Gastrointestinal reactions were the most common reason leading to discontinuation of study product during Initial Dose Escalation and Up-Dosing combined (6.5% PALFORZIA, 1.0% placebo), followed by respiratory disorders (2.3% PALFORZIA, 1.0% placebo) in Studies 1 and 2.

The timing of symptoms relative to exposure to PALFORZIA was evaluated for dosing that occurred within a clinical setting during Initial Dose Escalation and on the day of initiation of each new dose level during the Up-Dosing phase (every 2 weeks) and during monthly Maintenance visits. Symptoms occurring in the clinic following any dose of PALFORZIA had a median time to onset of 4 minutes for 502 subjects (70.8%). The median time to resolution of the last symptom was 37 minutes.

Study 3 (NCT03736447) was a randomized, double-blind, placebo-controlled efficacy and safety study conducted in the United States and Europe evaluating PALFORZIA versus placebo in 146 subjects aged 1 through 3 years with peanut allergy. The primary efficacy analysis population consisted of 98 subjects who received at least one dose of study treatment. In this study, eligible subjects were those sensitive to > 3 mg and ≤ 300 mg of peanut protein at the screening DBPCFC. Of the subjects treated with PALFORZIA in the primary analysis population, 13.3% had a medical history of allergic rhinitis, 72.4% reported multiple food allergies, 63.3% had a medical history of atopic dermatitis, and 9.6% had a present or previous diagnosis of asthma. The median age of subjects was 2 years. More than half of the subjects were male (58.2%). Most subjects were White (67.3%), Asian (16.4%), or Black or African American (3.4%) and most were not Hispanic or Latino (72.6%).

In Study 3, the most common adverse reactions in subjects treated with PALFORZIA (incidence ≥ 5%) were gastrointestinal, respiratory, and skin symptoms commonly associated with allergic reactions, as shown in Table 6.

Table 6: Treatment-Emergent Adverse Reactions in ≥ 5% of PALFORZIA-Treated Subjects (Aged 1 through 3 Years)

System Organ Class / Preferred Term [1]	IDE PALFORZIA (N = 98)	IDE Placebo (N = 48)	Up-Dosing PALFORZIA (N = 98)	Up-Dosing Placebo (N = 48)	300 mg PALFORZIA (N = 87)	300 mg Placebo (N = 45)
Respiratory, thoracic and mediastinal disorders						
Cough	2 (2.0%)	0 (0.0%)	17 (17.3%)	2 (4.2%)	4 (4.6%)	0 (0.0%)
Sneezing	4 (4.1%)	0 (0.0%)	14 (14.3%)	5 (10.4%)	2 (2.3%)	2 (4.4%)
Rhinitis [2]	3 (3.1%)	1 (2.1%)	9 (9.2%)	1 (2.1%)	5(5.7%)	0 (0.0%)
Nasal congestion	4 (4.1%)	0 (0.0%)	3 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Throat irritation	1 (1.0%)	1 (2.1%)	4 (4.1%)	1 (2.1%)	3 (3.4%)	0 (0.0%)
Wheezing [3]	0 (0.0%)	0 (0.0%)	4 (4.1%)	1 (2.1%)	1 (1.1%)	0 (0.0%)
Gastrointestinal disorders						
Abdominal pain [4]	0 (0.0%)	1 (2.1%)	15 (15.3%)	2 (4.2%)	7 (8.0%)	1 (2.2%)
Vomiting [5]	0 (0.0%)	0 (0.0%)	13 (13.3%)	0 (0.0%)	4(4.6%)	0 (0.0%)
Diarrhea [6]	1 (1.0%)	1 (2.1%)	9 (9.2%)	5 (10.4%)	3 (3.4%)	0 (0.0%)
Oral pruritus [7]	0 (0.0%)	0 (0.0%)	4 (4.1%)	1 (2.1%)	7 (8.0%)	0 (0.0%)
Oropharyngeal pain [8]	1 (1.0%)	0 (0.0%)	3 (3.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders						
Urticaria [9]	5 (5.1%)	1 (2.1%)	27 (27.6%)	13 (27.1%)	9 (10.3%)	2 (4.4%)
Rash [10]	2 (2.0%)	2 (4.2%)	26 (26.5%)	11 (22.9%)	7 (8.0%)	1 (2.2%)
Pruritus [11]	2 (2.0%)	0 (0.0%)	14 (14.3%)	12 (25.0%)	2 (2.3%)	1 (2.2%)
Perioral dermatitis	1 (1.0%)	0 (0.0%)	6 (6.1%)	0 (0.0%)	4 (4.6%)	0 (0.0%)

Treatment-emergent adverse reactions are included in the table if they occurred in ≥ 5% of PALFORZIA-treated subjects across all dosing phases combined. Data across all dosing phases combined are not shown.
At each level of summarization (any event, system organ class, and preferred term), subjects with more than 1 adverse reaction were counted only once within study period.
[1] Adverse reactions were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.
[2] Includes preferred terms of rhinorrhea, rhinitis and rhinitis allergic.
[3] Includes preferred terms of wheezing and stridor.
[4] Includes preferred term of abdominal pain, abdominal pain upper, and abdominal discomfort.
[5] Includes preferred terms of vomiting and regurgitation.
[6] Includes preferred terms of diarrhea and frequent bowel movements.
[7] Includes preferred terms of oral pruritus, tongue pruritis, and lip pruritus.
[8] Includes preferred terms of oropharyngeal pain, oral discomfort, odynophagia, and oral pain.
[9] Includes preferred terms of urticaria and urticaria papular.
[10] Includes preferred terms of rash, rash erythematous, rash generalized, rash macular, rash papular, rash pruritic, eczema, erythema, and papule.
[11] Includes preferred terms of pruritus, pruritus generalized, ear pruritus, eye pruritus, and nasal pruritus.

In Study 3, anaphylactic reaction was reported in 8 (8.2%) PALFORZIA-treated subjects (in no subjects during Initial Dose Escalation, 2 subjects during Up-Dosing, and 6 subjects during Maintenance) and 4 (8.3%) placebo-treated subjects (in no subjects during Initial Dose Escalation, 2 subjects during Up-Dosing, and 2 subjects during Maintenance). Out of the 9 total anaphylactic reaction events in 8 PALFORZIA-treated subjects, 3 were related to PALFORZIA, all during Up-Dosing, and 6 were to other food allergens *[see Warnings and Precautions (5.1)]*.

A total of 15 (15.3%) PALFORZIA-treated subjects and 3 (6.3%) placebo-treated subjects discontinued for any reason in Study 3. Adverse reactions led to study discontinuation in 5.1% PALFORZIA-treated subjects and no placebo-treated subjects during Up-Dosing in Study 3, and 2.3% PALFORZIA-treated subjects and no placebo-treated subjects during Maintenance dosing in Study 3. Gastrointestinal reactions were the most common reason leading to discontinuation of study

product during Up-Dosing (3.1% PALFORZIA, none in placebo), followed by respiratory disorders (3.1% PALFORZIA, none in placebo) in Study 3. No PALFORIZA-treated subjects discontinued during IDE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PALFORZIA during pregnancy. Women exposed to PALFORZIA during pregnancy, or their health care professionals are encouraged to contact Aimmune by calling 1-833-246-2566.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. No human or animal data are available to establish the presence or absence of the risks due to PALFORZIA in pregnant women.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Anaphylaxis may occur following accidental exposure to peanut in peanut-allergic pregnant women. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus.

Maternal adverse reactions

PALFORZIA may cause anaphylaxis *[see Warnings and Precautions (5.1) and Fetal/Neonatal adverse reactions]*.

Fetal/Neonatal adverse reactions

PALFORZIA may cause anaphylaxis *[see Warnings and Precautions (5.1)]*. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus.

8.2 Lactation

Risk Summary

There are no data available on the presence of PALFORZIA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for PALFORZIA and any other potential adverse effects on the breastfed child from PALFORZIA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of PALFORZIA have not been established in persons younger than 1 year of age.

10 OVERDOSAGE

Symptoms of overdose in patients with peanut allergy may include hypersensitivity reactions such as anaphylaxis or local gastrointestinal allergic reactions *[see Warnings and Precautions (5.1 and 5.5)]*. In case of severe symptoms such as difficulty in swallowing, difficulty in breathing, changes in voice, feeling of fullness in the throat, or anaphylaxis, patients should be instructed to use epinephrine and seek immediate medical assistance *[see Warnings and Precautions (5.1)* and *Patient Counseling Information (17)]*.

11 DESCRIPTION

PALFORZIA [Peanut (*Arachis hypogaea*) Allergen Powder-dnfp] is a powder for oral administration. PALFORZIA is manufactured from defatted peanut flour. PALFORZIA is available in capsules containing 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg peanut protein, and a sachet containing 300 mg peanut protein. Each dose meets specifications for quantities of Ara h 1, Ara h 2, and Ara h 6, measured by immunoassay alone or in combination with high performance liquid chromatography.

Depending on the dose level, PALFORZIA 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, and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of PALFORZIA has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PALFORZIA has not been evaluated for carcinogenicity, genotoxicity, mutagenic potential, or impairment of male or female fertility in animals.

14 CLINICAL STUDIES

The efficacy of PALFORZIA for the mitigation of allergic reactions, including anaphylaxis, in patients 4 through 17 years of age with peanut allergy was investigated in Study 1 (NCT02635776). Study 1 was a phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of

PALFORZIA in patients with peanut allergy aged 4 through 55 years in the United States, Canada, and Europe. The primary analysis population consisted of 496 subjects (PALFORZIA, N = 372; placebo, N = 124) aged 4 through 17 years in the intent-to-treat (ITT) population who received at least 1 dose of study treatment. After an Initial Dose Escalation ranging from 0.5 mg to 6 mg on Day 1 and confirmation of tolerability of the 3 mg dose on Day 2, subjects underwent Up-Dosing for 20-40 weeks starting at 3 mg until the 300 mg dose was reached. The Up-Dosing period varied for each subject depending on how the dose was tolerated. Subjects then underwent 24-28 weeks of Maintenance immunotherapy with 300 mg PALFORZIA until the end of the study. At the end of the Maintenance period, subjects completed an exit DBPCFC to approximate an accidental exposure to peanut and to assess their ability to tolerate increasing amounts of peanut protein with no more than mild allergic symptoms.

The primary efficacy endpoint was the percentage of subjects tolerating a single dose of 600 mg peanut protein in the exit DBPCFC with no more than mild allergic symptoms after 6 months of Maintenance treatment. The primary efficacy endpoint was considered met if the lower bound of the 95% confidence interval (CI) for the difference in response rates between the treatment and the placebo groups was greater than the prespecified margin of 15%. Key secondary endpoints included the comparisons of the response rates after single doses of 300 mg and 1000 mg peanut protein as well as a comparison of the maximum severity of symptoms at any challenge dose of peanut protein during the exit DBPCFC. The key secondary endpoints were to be evaluated for statistical significance (two-sided $p < 0.05$) only if the primary endpoint and all the preceding tests in the hierarchy were statistically significant in favor of PALFORZIA. Response rates at the exit DBPCFC for the ITT population are shown in Table 7. The maximum severity of symptoms at any challenge is shown in Table 8.

Table 7: Response Rates at the Exit DBPCFC in Study 1 (ITT Population, 4 through 17 Years)

Peanut challenge dose, single dose	**300 mg [1]**	**600 mg [2]**	**1000 mg [1]**
PALFORZIA (N = 372)	76.6%	67.2%	50.3%
Placebo (N = 124)	8.1%	4.0%	2.4%
Treatment difference (95% CI)	68.5% (58.6%, 78.5%)	63.2% (53.0%, 73.3%)	47.8% (38.0%, 57.7%)
P-value	< 0.0001	< 0.0001	< 0.0001

Subjects without an exit DBPCFC were counted as non-responders.

[1] Secondary endpoint was considered met if the Farrington-Manning test for a non-zero treatment difference was significant at the two-sided 0.05 level.

[2] The primary efficacy endpoint was considered met if the lower bound of the Farrington-Manning 95% CI was greater than the prespecified margin of 15 percentage points.

CI, confidence interval, DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat.

Table 8: Maximum Severity of Symptoms at Any Challenge Dose During the Exit DBPCFC (ITT Population, 4 through 17 Years)

Symptom Severity	PALFORZIA N = 372	Placebo N = 124
None	37.6%	2.4%
Mild	32.0%	28.2%
Moderate	25.3%	58.9%
Severe [1]	5.1%	10.5%

Subjects without an exit DBPCFC were assigned the maximum severity during the screening DBPCFC, which equates to no change from screening.

P-value < 0.0001; symptom severity was assigned with equally spaced scores (e.g., 0, 1, 2, and 3 for none, mild, moderate, and severe, respectively), and the difference of mean scores between the two treatment arms was tested using the Cochran-Mantel-Haenszel statistic stratified by geographic region (North America, Europe).

[1] Includes severe symptoms and life-threatening or fatal reactions. No subjects had symptoms considered life-threatening or fatal.

DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat.

The completer population consisted of all subjects aged 4 through 17 years in the ITT population who stayed on treatment and had an evaluable exit DBPCFC (296 PALFORZIA, 116 placebo). In the completer population, the proportion of subjects who tolerated single highest doses of 300 mg, 600 mg, and 1000 mg with no more than mild symptoms at the exit DBPCFC were 96.3%, 84.5%, and 63.2%, respectively for PALFORZIA-treated subjects compared with 8.6%, 4.3%, and 2.6% for placebo-treated subjects.

The efficacy of PALFORZIA for the mitigation of allergic reactions, including anaphylaxis, in subjects 1 through 3 years of age with peanut allergy was investigated in Study 3 (NCT03736447). Study 3 was a phase 3, international, randomized, double-blind, placebo-controlled study of the efficacy and safety of PALFORZIA in subjects with peanut allergy aged 1 through 3 years in the United States, and Europe. The primary analysis population consisted of 146 subjects (PALFORZIA, N = 98; placebo, N = 48) aged 1 through 3 years in the ITT population who received at least 1 dose of study treatment. After an Initial Dose Escalation ranging from 0.5 mg to 3 mg on Day 1 and confirmation of tolerability of the 1 mg dose on Day 2, subjects underwent Up-Dosing for 20-40 weeks starting at 1 mg until the 300 mg dose was reached. The Up-Dosing period varied for each subject depending on how the dose was tolerated. Subjects then underwent 12-24 weeks of Maintenance immunotherapy with 300 mg PALFORZIA until the end of the study. At the end of the Maintenance period, subjects completed an exit DBPCFC to approximate an accidental exposure to peanut and to assess their ability to tolerate increasing amounts of peanut protein with no more than mild allergic symptoms.

The primary efficacy endpoint was the percentage of subjects tolerating a single dose of 600 mg peanut protein in the exit DBPCFC with no more than mild allergic symptoms after 6 months of Maintenance treatment. The primary efficacy endpoint was considered met if the lower bound of the 95% confidence interval (CI) for the difference in response rates between the treatment and the placebo groups was greater than the prespecified margin of 15%. Key secondary endpoints included the comparisons of the response rates after single doses of 300 mg and 1000 mg peanut protein as well as a comparison of the maximum severity of symptoms at any challenge dose of peanut protein during the exit DBPCFC (up to 2000 mg). The key secondary endpoints were to be evaluated for statistical significance (two-sided $p < 0.05$) only if the primary endpoint and all the preceding tests in the hierarchy were statistically significant in favor of PALFORZIA. Response rates at the exit DBPCFC for the ITT population are shown in Table 9. The maximum severity of symptoms at any challenge is shown in Table 10.

Table 9: Response Rates at the Exit DBPCFC in Study 3 (ITT Population, 1 through 3 Years)

Peanut challenge dose, single dose	300 mg [1]	600 mg [2]	1000 mg [1]
PALFORZIA (N = 98)	79.6%	73.5%	68.4%
Placebo (N = 48)	22.9%	6.3%	4.2%
Treatment difference (95% CI)	56.7% (39.8%, 73.5%)	67.2% (50.0%, 84.5%)	64.2% (47.0%, 81.4%)
P-value	< 0.0001	< 0.0001	< 0.0001

Subjects without an exit DBPCFC were counted as non-responders.

[1] Secondary endpoint was considered met if the Farrington-Manning test for a non-zero treatment difference was significant at the two-sided 0.05 level.

[2] The primary efficacy endpoint was considered met if the lower bound of the Farrington Manning 95% CI was greater than the prespecified margin of 15 percentage points.

CI: confidence interval, DBPCFC: double-blind, placebo-controlled food challenge; ITT: intent-to-treat.

Table 10: Maximum Severity of Symptoms at Any Challenge Dose During the Exit DBPCFC (ITT Population, 1 through 3 Years)

Symptom Severity	PALFORZIA N = 98	Placebo N = 48
None	51.0%	4.2%
Mild	29.6%	47.9%
Moderate	17.3%	43.8%
Severe [1]	2.0%	4.2%

Subjects without an exit DBPCFC were assigned the maximum severity during the screening DBPCFC, which equates to no change from screening.

P-value < 0.0001; symptom severity was assigned with equally spaced scores (e.g., 0, 1, 2, and 3 for none, mild, moderate, and severe, respectively), and the difference of mean scores between the two treatment arms was tested using the Cochran-Mantel-Haenszel statistic stratified by geographic region (North America, Europe).

[1] Includes severe symptoms and life-threatening or fatal reactions. No subjects had symptoms considered life-threatening or fatal.

DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat.

The completer population consisted of all subjects aged 1 through 3 years in the ITT population who stayed on treatment and had an evaluable exit DBPCFC (83 PALFORZIA, 45 placebo). In the completer population, the proportion of subjects who tolerated single highest doses of 300 mg, 600 mg, and 1000 mg, with no more than mild symptoms at the exit DBPCFC were 94.0%, 86.7%, and 80.7%, respectively for PALFORZIA-treated subjects compared with 24.4%, 6.7%, and 4.4%, for placebo-treated subjects.

There are no data available on the efficacy of PALFORZIA in individuals who did not progress onto Maintenance therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

Table 11: PALFORZIA Commercial Packaging Presentations

Packaging Presentation	Kit Components (Capsules or Sachets)	Number of Doses per Kit	NDC Numbers (Kit Components)	NDC Number (Kit)
Initial Dose Escalation (1-3 years)	Each pack contains 7 capsules: ● 0.5 mg (Level A) One 0.5 mg capsule ● 1 mg (Level B) One 1 mg capsule ● 1.5 mg (Level C) One 0.5 mg capsule; One 1 mg capsule ● 3 mg (Level D) Three 1 mg capsules	4	 71881-121-01 71881-122-01 71881-121-01 71881-122-01 71881-122-01	71881-113-07
Initial Dose Escalation (4-17 years)	Each pack contains 13 capsules: ● 0.5 mg (Level A) One 0.5 mg capsule ● 1 mg (Level B) One 1 mg capsule ● 1.5 mg (Level C) One 0.5 mg capsule; One 1 mg capsule ● 3 mg (Level D) Three 1 mg capsules ● 6 mg (Level E) Six 1 mg capsules	5	 71881-121-01 71881-122-01 71881-121-01 71881-122-01 71881-122-01 71881-122-01	71881-113-13
Up-Dosing				
1 mg (Level 0)	Fifteen 1 mg capsules	15	71881-122-01	71881-100-15
3 mg (Level 1)	Forty-five 1 mg capsules	15	71881-122-01	71881-101-45
6 mg (Level 2)	Ninety 1 mg capsules	15	71881-122-01	71881-102-90
12 mg (Level 3)	Thirty 1 mg capsules; Fifteen 10 mg capsules	15	71881-122-01 71881-123-01	71881-103-45
20 mg (Level 4)	Fifteen 20 mg capsules	15	71881-124-01	71881-104-15
40 mg (Level 5)	Thirty 20 mg capsules	15	71881-124-01	71881-105-30
80 mg (Level 6)	Sixty 20 mg capsules	15	71881-124-01	71881-106-60
120 mg (Level 7)	Fifteen 20 mg capsules; Fifteen 100 mg capsules	15	71881-124-01 71881-125-01	71881-107-30
160 mg (Level 8)	Forty-five 20 mg capsules; Fifteen 100 mg capsules	15	71881-124-01 71881-125-01	71881-108-60
200 mg (Level 9)	Thirty 100 mg capsules	15	71881-125-01	71881-109-30
240 mg (Level 10)	Thirty 20 mg capsules; Thirty 100 mg capsules	15	71881-124-01 71881-125-01	71881-110-60

Packaging Presentation	Kit Components (Capsules or Sachets)	Number of Doses per Kit	NDC Numbers (Kit Components)	NDC Number (Kit)
300 mg (Level 11)	Fifteen 300 mg sachets	15	71881-111-01	71881-111-15
Maintenance				
300 mg (Level 11)	Thirty 300 mg sachets	30	71881-111-01	71881-111-30
300 mg (Level 11)	Ninety 300 mg sachets (Three cartons containing Thirty 300 mg sachets each)	90	71881-111-01	71881-111-90

NDC, National Drug Code.

Table 12: PALFORZIA Office Dose Kit Packaging Presentations

Packaging Presentation	Kit Components (Blisters, Capsules, or Sachets)	Number of Doses per Kit	NDC Numbers (Kit Components)	NDC Number (Kit)
1 mg (Level 0)	Eighteen blisters, each containing: One 1 mg capsule	18	71881-100-09 71881-122-01	71881-100-99
3 mg (Level 1)	Eighteen blisters, each containing: Three 1 mg capsules	18	71881-101-09 71881-122-01	71881-101-99
6 mg (Level 2)	Eighteen blisters, each containing: Six 1 mg capsules	18	71881-102-09 71881-122-01	71881-102-99
12 mg (Level 3)	Twelve blisters, each containing: Two 1 mg capsules One 10 mg capsule	12	71881-103-09 71881-122-01 71881-123-01	71881-103-99
20 mg (Level 4)	Twelve blisters, each containing: One 20 mg capsule	12	71881-104-09 71881-124-01	71881-104-99
40 mg (Level 5)	Twelve blisters, each containing: Two 20 mg capsules	12	71881-105-09 71881-124-01	71881-105-99
80 mg (Level 6)	Twelve blisters, each containing: Four 20 mg capsules	12	71881-106-09 71881-124-01	71881-106-99
120 mg (Level 7)	Twelve blisters, each containing: One 20 mg capsule One 100 mg capsule	12	71881-107-09 71881-124-01 71881-125-01	71881-107-99
160 mg (Level 8)	Twelve blisters, each containing: Three 20 mg capsules One 100 mg capsule	12	71881-108-09 71881-124-01 71881-125-01	71881-108-99
200 mg (Level 9)	Twelve blisters, each containing: Two 100 mg capsules	12	71881-109-09 71881-125-01	71881-109-99
240 mg (Level 10)	Twelve blisters, each containing: Two 20 mg capsules Two 100 mg capsules	12	71881-110-09 71881-124-01 71881-125-01	71881-110-99
300 mg (Level 11)	Fifteen 300 mg sachets	15	71881-111-09	71881-111-99

NDC, National Drug Code.

Store PALFORZIA in the original packaging at 2° to 25°C (36° to 77°F). Avoid excessive heat. Do not freeze. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patient, parent, or guardian to read the FDA-approved patient labeling (Medication Guide).

Advise patient, parent, or guardian that patient should follow a strict peanut-avoidant diet.

Advise patient, parent, or guardian that PALFORZIA will not mitigate allergic reactions to other foods to which they might be allergic.

Allergic Reactions

Advise patient, parent, or guardian that PALFORZIA may cause allergic reactions, including anaphylaxis that may be life-threatening. Educate patient, parent, or guardian to recognize the signs and symptoms of an allergic reaction *[see Warnings and Precautions (5.1)]*. The signs and symptoms of a severe allergic reaction may include syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.

Ensure patient has injectable epinephrine and instruct patient, parent, or guardian on its proper use and that injectable epinephrine must be available for immediate use at all times. Instruct patient, parent, or guardian that if patient experiences a severe allergic reaction to seek immediate medical care, discontinue PALFORZIA, and resume treatment only when advised by their health care professional *[see Warnings and Precautions (5.1)]*.

Advise patient, parent, or guardian to read the patient information for epinephrine.

Inform patient, parent, or guardian that the first dose of each new Up-Dosing level of PALFORZIA must be administered in a health care setting under the supervision of a health care professional, and that after consuming PALFORZIA, patient will be monitored for signs and symptoms of an allergic reaction *[see Warnings and Precautions (5.1)]*.

Advise patient, parent, or guardian that if patient experiences an escalating or persistent allergic reaction or becomes intolerant to PALFORZIA at home to contact their health care professional immediately.

Administration of PALFORZIA to young patients should be under adult supervision *[see Dosage and Administration (2)]*.

PALFORZIA REMS Program

Advise patient, parent, or guardian that due to the risk of anaphylaxis, PALFORZIA is only available through a restricted program called the PALFORZIA REMS Program *[see Warnings and Precautions (5.2)]*.

Inform patient, parent, or guardian of the following requirements:

- Patient must be enrolled in the PALFORZIA REMS Program.
- Patient, parent or guardian must be educated on the need for monitoring with the Initial Dose Escalation and first dose of each new Up-Dosing level and how to recognize the signs and symptoms of anaphylaxis.
- Patient must continue dietary peanut avoidance.
- Injectable epinephrine must be available to patient for immediate use at all times.

Asthma

Instruct patient, parent, or guardian that patients with asthma should stop taking PALFORZIA and contact their health care professional immediately if they have difficulty breathing or if their asthma becomes difficult to control *[see Warnings and Precautions (5.3)]*.

Eosinophilic Esophagitis

Because of the risk of eosinophilic esophagitis instruct patient, parent, or guardian that patients with severe or persistent symptoms of esophagitis or gastrointestinal intolerance should discontinue PALFORZIA and contact their health care professional *[see Warnings and Precautions (5.4 and 5.5)]*.

Handling Instructions

Advise patient, parent, or guardian of the following:

- To store PALFORZIA at room temperature or in a refrigerator. Do not freeze.
- That patient must not swallow capsule(s) or inhale the powder.
- To open capsule(s) or sachet and empty the entire dose onto a few spoonfuls of refrigerated or room temperature semisolid food (e.g., applesauce, yogurt, pudding) and to mix well. Do not use liquid (e.g., milk, water, juice) to prepare PALFORZIA for consumption.
- That patient should consume the entire prepared mixture.
- To dispose of all unused PALFORZIA *[see Dosage and Administration (2.3)].*
- To dispose of the opened capsule(s) or sachet and wash hands immediately after handling.

Dosing Instructions

Advise patient, parent, or guardian of the following:

- The importance of taking each dose daily to avoid loss of treatment effect.
- That each dose should be consumed with a meal, at approximately the same time each day, preferably in the evening.
- To observe the patient for at least 60 minutes after administering PALFORZIA for any signs of intolerability.
- To contact their health care professional for advice on how to resume PALFORZIA if doses are missed.
- That the risk of an allergic reaction following PALFORZIA administration may be increased in the presence of cofactors such as:
    - Exercise or hot water exposure (e.g., a hypermetabolic state)
    - A medical event such as an intercurrent illness (e.g., viral infection)
    - Fasting
    - Menstruation
    - Sleep deprivation
    - Nonsteroidal anti-inflammatory drug use
    - Uncontrolled asthma

    Temporarily withholding or decreasing PALFORZIA doses may be required in the presence of these cofactors.

Patient should delay consuming PALFORZIA after strenuous exercise until signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) have subsided and avoid taking hot showers or baths immediately prior to or within 3 hours after consuming PALFORZIA.

Manufactured by:
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