SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

PALFORZIA 300 mg oral powder in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PALFORZIA 300 mg oral powder in capsules for opening

Each capsule contains 300 mg peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to beige oral powder in capsules for opening or sachet.

PALFORZIA 300 mg oral powder in sachet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PALFORZIA is indicated for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. PALFORZIA may be continued in patients 18 years of age and older.

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

4.2 Posology and method of administration

This medicine should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases.

Initial dose escalation and the first dose of each new up-dosing level are to be administered in a health care setting prepared to manage potential severe allergic reactions.

Self-injectable adrenaline (epinephrine) must be available to the patient at all times.

Posology

Treatment with PALFORZIA is administered in 3 sequential phases: Initial dose escalation, up-dosing, and maintenance.

For each dose level during up-dosing, the doses given in clinic and at home should be from the same batch to avoid variations in the potency range (see section 4.4).

The dose configurations for each phase of dosing are provided in Table 1, Table 2, and Table 3.

A dose level can be considered tolerated if no more than transient symptoms are observed with no or minimal medical intervention/therapy required.

Initial dose escalation phase

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 0.5 mg and completing with 6 mg (see Table 1).

Table 1: Dose and capsule presentation for initial dose escalation

Dose	Capsule presentation per dose
0.5 mg	1 × 0.5 mg capsule
1 mg	1 × 1 mg capsule
1.5 mg	1 × 0.5 mg capsule + 1 × 1 mg capsule
3 mg	3 × 1 mg capsules
6 mg	6 × 1 mg capsules

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

No dose level should be omitted.

Patients must be observed after the last dose for at least 60 minutes until suitable for discharge.

Treatment must be discontinued if symptoms requiring medical intervention (e.g., use of adrenaline) occur with any dose during initial dose escalation.

Patients who tolerate at least the 3 mg single dose PALFORZIA during initial dose escalation must return to the health care setting for initiation of up-dosing.

If possible, up-dosing should begin the day after initial dose escalation.

If the patient is unable to begin up-dosing within 4 days, initial dose escalation should be repeated in a health care setting.

Up-dosing phase

Initial dose escalation must be completed before starting up-dosing.

Up-dosing consists of 11 dose levels and is initiated at a 3 mg dose (see Table 2).

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. Patients should be observed for at least 60 minutes after administering the first dose of a new up-dosing level until suitable for discharge.

If the patient tolerates the first dose of the increased dose level, the patient may continue that dose level at home.

All the dose levels in Table 2 must be administered in sequential order at 2-week intervals if tolerated. No dose level should be omitted. Patients must not progress through up-dosing more rapidly than shown in Table 2.

Table 2: Daily dosing configuration for up-dosing

Dose level	Total daily dose	Presentation of dose (capsule colour)	Dose duration (weeks)
1	3 mg	3 × 1 mg capsules (red)	2
2	6 mg	6 × 1 mg capsules (red)	2
3	12 mg	2 × 1 mg capsules (red) 1 × 10 mg capsule (blue)	2
4	20 mg	1 × 20 mg capsule (white)	2
5	40 mg	2 × 20 mg capsules (white)	2
6	80 mg	4 × 20 mg capsules (white)	2
7	120 mg	1 × 20 mg capsule (white) 1 × 100 mg capsule (red)	2
8	160 mg	3 × 20 mg capsules (white) 1 × 100 mg capsule (red)	2
9	200 mg	2 × 100 mg capsules (red)	2
10	240 mg	2 × 20 mg capsules (white) 2 × 100 mg capsules (red)	2
11	300 mg	1 × 300 mg sachet	2

No more than one dose should be consumed per day. Patients should be instructed not to consume a dose at home on the same day as a dose consumed in the clinic.

Care should be taken to ensure that patients have only one dose level in their possession at any time.

Dose modification or discontinuation should be considered for patients who do not tolerate up-dosing as described in Table 2 (see *Dose modification instructions*).

Maintenance therapy

All dose levels of up-dosing must be completed before starting maintenance.

The maintenance dose of PALFORZIA is 300 mg daily.

Table 3: Daily dosing configuration for maintenance

Presentation of dose	Total daily dose
1 × 300 mg sachet	300 mg

Daily maintenance is required to maintain the tolerability and clinical effects of PALFORZIA.

Efficacy data currently are available for up to 24 months of treatment with PALFORZIA. No recommendation can be made about the duration of treatment beyond 24 months.

The effect of stopping treatment on maintenance of clinical efficacy has not been evaluated.

If treatment with PALFORZIA is stopped, patients must continue to carry self-injectable adrenaline at all times.

Dose modification instructions

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 or for practical reasons for 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. Clinical judgment should be used to determine the best course of action on a patient by patient basis. This can include maintaining the dose level for longer than 2 weeks, reducing, or withholding PALFORZIA doses.

Management of consecutive missed doses

Missed doses of PALFORZIA may pose a significant risk to patients due to potential loss of desensitisation. The guidelines in Table 4 are to be used for managing missed doses.

Table 4: Management of consecutive missed doses

Consecutive missed doses	**Action**
1 to 2 days	Patients may resume treatment at the same dose level at home.
3 to 4 days	Patients may resume treatment at the same dose level under medical supervision in a health care setting based on medical judgment.
5 to 14 days	Patients may resume up-dosing with PALFORZIA under medical supervision in a health care setting at a dose of 50% or less of the last tolerated dose.
Greater than 14 days	Patient compliance should be evaluated and it should be considered to re-start up-dosing at 3 mg under supervision in a health care setting or to discontinue treatment completely.

Following a dose reduction due to missed doses, up-dosing should be resumed as described in Table 2.

Special populations

Elderly

The safety and efficacy of PALFORZIA therapy initiated in patients aged over 17 years has not been established.

Paediatric population

The safety and efficacy of PALFORZIA therapy in children aged less than 4 years have not yet been established. No data are available.

Method of administration

The powder must be taken orally after mixing with an age-appropriate soft food.

Capsules are not to be ingested. Inhalation of the powder must be avoided.

To empty the contents of each capsule, the two ends of the capsule should be pulled apart gently, and gently rolled between the finger and thumb. Sachets should be opened by carefully cutting or tearing along the line indicated.

The entire dose of PALFORZIA powder should be emptied onto a few spoonfuls of refrigerated or room temperature semisolid food (e.g., fruit puree, yogurt, rice-pudding) and mixed well. Liquid (e.g., milk, water, juice) must not be used.

Hands should be washed immediately after handling PALFORZIA capsule(s) or sachets.

Each dose taken at home should be consumed daily with a meal at approximately the same time each day, preferably in the evening. PALFORZIA should not be taken on an empty stomach or after fasting.

Alcohol should not be taken for 2 hours before or 2 hours after a dose (see section 4.4, Table 5).

PALFORZIA should not be taken within 2 hours of bedtime.

4.3 Contraindications

- Current severe or uncontrolled asthma
- A history of, or current, eosinophilic oesophagitis (EoE); other eosinophilic gastrointestinal disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); dysphagia
- A history of, or current, severe mast cell disorder
- Severe or life-threatening anaphylaxis within 60 days before initiating treatment with PALFORZIA
- Hypersensitivity to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

PALFORZIA is not intended for, and does not provide, immediate relief of allergic symptoms. Therefore, this medicinal product is not to be used for emergency treatment of allergic reactions, including anaphylaxis.

Patients should not have active wheezing, uncontrolled severe atopic disease (e.g., atopic dermatitis or eczema), a flare of atopic disease or suspected intercurrent illness prior to initiation of therapy.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Adrenaline

Self-injectable adrenaline must be prescribed to patients receiving this medicinal product. Patients must be instructed to carry self-injectable adrenaline at all times. Patients and caregivers must be instructed to recognise the signs and symptoms of an allergic reaction and in the proper use of self-injectable adrenaline. Patients should be instructed to seek immediate medical care upon its use and to stop treatment until they have been evaluated by a physician.

PALFORZIA may not be suitable for patients who are taking medications that can inhibit or potentiate the effect of adrenaline (see the SmPC of adrenaline for further information).

Systemic allergic reactions including anaphylaxis

When treated with PALFORZIA, peanut-allergic patients are exposed to peanut allergens that cause allergic symptoms. Therefore, allergic reactions to this medicinal product are expected in these patients. These reactions mostly occur during the first 2 hours after ingestion of the dose and are usually mild or moderate; however, more severe reactions may occur. Patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment.

Dose modifications should be considered for patients who experience moderate or severe adverse allergic reactions to PALFORZIA. For dose modification instructions, see section 4.2.

PALFORZIA can cause systemic allergic reactions including anaphylaxis, which may be life-threatening.

Severe adverse reactions such as difficulty swallowing, difficulty breathing, changes in voice or feeling of fullness in the throat, dizziness or fainting, severe stomach cramps or pain, vomiting, diarrhoea, or severe flushing or itching of the skin require immediate treatment, including use of adrenaline and subsequent medical evaluation.

Patients must be educated to recognise the signs and symptoms of allergic reactions. Patients and caregivers should be instructed to contact a health care professional before administering the next dose of PALFORZIA if symptoms of an escalating or persistent allergic reaction occur. Any reaction must be treated promptly (e.g., with self-administration of intramuscular adrenaline) in case a severe adverse reaction develops and immediate medical attention should be sought directly afterwards. In the emergency department, treatment should follow the anaphylaxis guidelines.

Patients may be more likely to experience allergy symptoms after dosing of PALFORZIA in the presence of a medical event such as an intercurrent illness (e.g., viral infection), exacerbation of asthma, or in the presence of other co-factors (e.g., exercise, menstruation, stress, fatigue, sleep deprivation, fasting, intake of nonsteroidal anti-inflammatory drugs or alcohol). Patients should be counselled proactively about the potential for the increased risk of anaphylaxis in the presence of these co-factors, which may be modifiable or non-modifiable. On an individual basis and when needed, the time of dosing should be adjusted to avoid modifiable cofactors. If it is not possible to avoid any of the modifiable cofactors or if affected by non-modifiable co-factors, withholding or decreasing the PALFORZIA dose temporarily should be considered. Table 5 provides guidance on recommended actions to mitigate the risks associated with co-factors whilst on treatment.

Table 5: Guidelines on management of co-factors

Modifiable co-factors	**Recommended action to be taken**
Hot bath or shower	Hot showers or baths should be avoided immediately prior to or following 3 hours of treatment.
Exercise	Exercise should be avoided immediately prior to or for 3 hours following treatment. After strenuous exercise signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) must have subsided before taking a dose.
Fasting or empty stomach	Each dose should be consumed with a meal.
Alcohol	Alcohol should not be taken for 2 hours before or 2 hours after a dose.
Intake of non-steroidal anti-inflammatory medicines	The potential for allergic reactions to occur if taking non-steroidal anti-inflammatory medicines whilst on PALFORZIA treatment should be considered.
Non-modifiable co-factors	
Intercurrent illness	Patients should be instructed to seek medical advice before taking their next dose of PALFORZIA.
Exacerbation of asthma	
Menstruation	Withholding or decreasing the PALFORZIA dose temporarily should be considered based on individual patient needs.
Stress	
Fatigue or sleep deprivation	

Desensitisation response

Strict daily, long-term dosing in conjunction with a peanut-avoidant diet is required to achieve desensitisation and maintain the treatment effect of PALFORZIA. Treatment interruptions, including non-daily dosing, may potentially lead to an increased risk of allergic reactions or even anaphylaxis.

As with any immunotherapy treatment, clinically meaningful desensitisation may not occur in all patients (see section 5.1).

Asthma

In patients with asthma, treatment may only be initiated when the asthma status is controlled. Treatment 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. Patients who have recurrent asthma exacerbations should be re-evaluated and discontinuation considered. This medicinal product has not been studied in patients on long-term systemic corticosteroid therapy.

Concomitant illnesses

This medicinal product may not be suitable for patients with certain medical conditions that may reduce the ability to survive a severe allergic reaction or increase the risk of adverse reactions after adrenaline administration. Examples of these medical conditions include, but are not limited to, markedly compromised lung function (chronic or acute; e.g., severe cystic fibrosis), unstable angina, recent myocardial infarction, significant arrhythmias, cyanotic congenital heart disease, uncontrolled hypertension, and inherited metabolic disorders.

Gastro-intestinal adverse reactions including eosinophilic oesophagitis (EoE)

If patients develop chronic or recurrent gastrointestinal symptoms, dose modification may be considered (see section 4.2). EoE has been reported in association with PALFORZIA (see section 4.8). For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia), the potential for a diagnosis of EoE should be considered. In patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, gastroesophageal reflux, chest pain, or abdominal pain, treatment must be discontinued and a diagnosis of EoE should be considered.

Concomitant allergen immunotherapy

This medicinal product has not been studied in patients receiving concomitant allergen immunotherapy. Caution should be exercised when administering this

medicinal product in conjunction with other allergen immunotherapies as the potential for severe allergic reactions may be enhanced.

Oral inflammation or wounds

Patients with acute severe inflammation of the mouth or oesophagus, or with oral wounds may be at greater risk of severe systemic allergic reactions following ingestion of peanut protein. Initiation of treatment should be postponed in these patients and ongoing treatment should be temporarily interrupted to allow healing of the oral cavity.

Chronic urticaria

Chronic urticaria, especially in the presence of severe exacerbations may confound the safety assessment of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Interactions with other medicinal products are not expected.

Severe allergic reactions may be treated with adrenaline (see section 4.4). Please refer to the SmPC for adrenaline for further information on medicines that may potentiate or inhibit the effects of adrenaline.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from defatted powder of *Arachis hypogaea L.*, semen (peanuts) in pregnant women.

Initiation of treatment with PALFORZIA is not recommended during pregnancy.

Treatment with this medicinal product may cause anaphylaxis, which is a risk to pregnant women. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a foetus during pregnancy. In addition, the effect of oral immunotherapy (OIT) on the immune system of the mother and foetus during pregnancy is unknown.

For patients who are established on OIT and become pregnant, the benefits of remaining on OIT and retaining desensitisation should be weighed against the risks of an anaphylactic reaction while remaining on OIT.

Breast-feeding

Peanut allergens have been found in human milk after consumption of peanuts. There are no data available on the effects of PALFORZIA 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 treatment and any other potential adverse effects on the breastfed child from PALFORZIA or from the underlying maternal condition.

Fertility

There are no specific clinical or nonclinical data on the effects of defatted powder of *Arachis hypogaea L.*, semen (peanuts) on fertility.

4.7 Effects on ability to drive and use machines

PALFORZIA has minor influence on the ability to drive and use machines. Caution should be exercised for 2 hours after dosing in case any symptoms of an allergic reaction occur that could impact the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (of any severity) are abdominal pain (49.4%), throat irritation (40.7%), pruritus (33.7%), nausea (33.2%), vomiting (28.5%), urticaria (28.5%), oral pruritus (26.0%), abdominal discomfort (22.9%), and abdominal pain upper (22.8%).

The incidence of adverse reactions was higher during up-dosing (85.7%) than initial dose escalation (45.1%) and maintenance (57.7%).

The median time from administration of PALFORZIA in a clinical setting to onset of the first symptom ranged from 4 to 8 minutes. The median time from onset of the first symptom to resolution of the last symptom ranged from 15 to 30 minutes.

10.5% of subjects discontinued study product due to 1 or more adverse reactions. The most common adverse reactions leading to discontinuation of treatment were abdominal pain (3.8%), vomiting (2.5%), nausea (1.9%), and systemic allergic reaction (1.6%), including anaphylaxis.

Tabulated list of adverse reactions

Table 6 is based on data from clinical trials. Listed adverse reactions are divided into groups according to the MedDRA system organ class and frequency. Frequency categories are defined as: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reaction**
Immune system disorders	*Very common*	Anaphylactic reaction (systemic allergic reaction; any severity)
	Common	Anaphylactic reaction, severe (anaphylaxis; systemic allergic reaction, severe)
Respiratory, thoracic, and mediastinal disorders	*Very common*	Throat tightness Cough Sneezing Throat irritation
	Common	Dyspnoea Wheezing
Gastrointestinal disorders	*Very common*	Vomiting Abdominal pain Abdominal pain upper Nausea Abdominal discomfort Paraesthesia oral Oral pruritus Lip pruritus
	Uncommon	Eosinophilic oesophagitis
Skin and subcutaneous tissue disorders	*Very common*	Urticaria Pruritus

Description of selected adverse reactions

Systemic allergic reactions (Anaphylactic reactions)

For the purpose of reporting the clinical study results, the term systemic allergic reaction is used to describe anaphylactic reaction events of any severity and the term anaphylaxis is used to distinguish anaphylactic reaction events that were severe.

Systemic allergic reactions of any severity were reported in 15.1% of subjects, including 0.6% during initial dose escalation, 8.7% during up-dosing, and 9.9% during maintenance. The majority of subjects who had systemic allergic reactions had reactions of mild or moderate severity. Severe systemic allergic reaction (anaphylaxis) was reported in 10 subjects (1.1% overall), including 4 subjects (0.4%) during up-dosing and 6 (0.8%) during maintenance at 300 mg/day. 1.6% discontinued due to systemic allergic reaction including 0.3% with anaphylaxis. Of the total population, 10.6% of subjects reported a single episode of systemic allergic reaction and 4.6% reported two or more systemic allergic reactions. Existing data suggest an increased risk of systemic allergic reaction for adolescents (21.9%) than for children (≤ 11 years; 11.9%).

In the clinical trials, the most commonly reported symptoms of systemic allergic reactions included skin disorders (urticaria, flushing, pruritis, face swelling, rash), respiratory disorders (dyspnea, wheezing, cough, throat tightness, rhinorrhea, throat irritation), and gastrointestinal disorders (abdominal pain, nausea, vomiting). The onset of most (87.0%) episodes of systemic allergic reaction was within 2 hours of the administration of the medication.

Adrenaline use

In the PALFORZIA safety population, 14.9% of subjects reported at least one episode of adrenaline use for any reason. 1.8% of patients reported at least one episode during initial dose escalation, 9.1% during up-dosing, and 8.7% during maintenance. Of subjects who reported adrenaline usage, 91.6% subjects required a single dose and 92.5% of adrenaline usage was for events of mild to moderate severity.

Eosinophilic oesophagitis (EoE)

In clinical trials, 12 out of 1,217 subjects were diagnosed with biopsy-confirmed eosinophilic oesophagitis while receiving PALFORZIA compared with 0 of 443 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 oesophagitis was resolved in 6 subjects and improved in 2 subjects.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Administration of PALFORZIA at greater than recommended doses in peanut-allergic patients increases the risk of side effects, including the risk of systemic allergic reactions or severe single-organ allergic reactions. In the event of anaphylaxis at home, patients should self-administer intramuscular adrenaline and follow-up with an emergency medical evaluation. In an emergency department, the anaphylaxis guidelines should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts, food
ATC code: V01AA08

Mechanism of action

The precise mechanism of desensitisation provided by defatted powder of *Arachis hypogaea L.*, semen (peanuts) is not fully understood.

A summary of immunoglobulin values reported for subjects aged 4 to 17 years treated with PALFORZIA for 12 months in the PALISADE study is provided in Table 7.

Table 7: Change over time in immunoglobulin values in PALISADE (ITT population, PALFORZIA subjects, 4-17 years)

Parameter	Statistic	Screening DBPCFC	End of up-dosing	Exit DBPCFC
ps-IgE (kUA/L)	n	372	305	272
	Geometric mean (SD) [1]	51.40 (5.965)	101.33 (8.134)	48.61 (7.799)
	Q1, Q3	18.6, 194.3	28.8, 491.0	12.2, 259.0
ps-IgG4 (mgA/L)	n	353	305	274
	Geometric mean (SD) [1]	0.538 (3.4655)	3.341 (4.0450)	5.557 (4.4633)
	Q1, Q3	0.22, 1.21	1.72, 8.79	2.50, 14.70
ps-IgE/ IgG4	n	353	305	272
	Geometric mean (SD) [1]	97.36 (5.053)	30.32 (4.640)	8.76 (5.261)
	Q1, Q3	36.2, 310.0	11.6, 88.4	2.3, 26.3

[1] Geometric means were calculated by computing the mean on the $\log_{10}$ scale and converting the mean to the original scale by calculating the antilog.

ITT, intent-to-treat; ps, peanut specific; Q1, Q3, first quartile, third quartile; DBPCFC, double-blind, placebo-controlled food challenge; SD, standard deviation.

In the ARTEMIS study, the geometric mean (SD) peanut specific IgE of the PALFORZIA group was 30.55 (7.794) kUA/L at the screening double-blind, placebo-controlled food challenge (DBPCFC), increasing to 44.28 (10.850) kUA/L at the end of Up-Dosing, thereafter decreasing to 28.92 (9.908) kUA/L at the exit DBPCFC (following 3 months of PALFORZIA maintenance dosing at 300 mg daily). The geometric LS (least squares) mean ratio (exit/screening) was 1.18, 95% confidence interval (CI) (0.97, 1.44).

Immunologic parameters in long-term maintenance

The sustained effects of PALFORZIA treatment on the immunologic parameters peanut-specific IgE, IgG4 and the IgE/IgG4 ratio for subjects who completed 12 and 18 months of PALFORZIA maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both PALISADE and the open-label follow-on study ARC004 are provided in Table 8.

Table 8: Immunologic parameters following continued maintenance at study exit (PALISADE and ARC004 completer populations, 4-17 years)

	PALISADE	ARC004	
	6-month maintenance	12-month maintenance	18-month maintenance
n, Geometric Mean (SD) [1]			
ps-IgE kUA/L	272	96	26
	48.61 (7.799)	27.87 (6.831)	13.42 (9.670)
ps-IgG4 mgA/L	274	89	25
	5.557 (4.4633)	5.875 (4.3605)	8.900 (3.1294)
ps-IgE/IgG4	272	89	25
	8.76 (5.261)	4.55 (6.189)	1.55 (5.462)

[1] Geometric means were calculated by computing the mean on the $\log_{10}$ scale and converting the mean to the original scale by calculating the antilog.

Clinical efficacy

In all PALFORZIA clinical studies, efficacy was measured using a DBPCFC. This food challenge was performed according to the Practical Allergy (PRACTALL) guidelines with modification to include a 600 mg protein dose (between the 300 mg and 1,000 mg challenge doses).

The efficacy of PALFORZIA was assessed in 2 randomised, double-blind, placebo-controlled, multicentre, phase 3 pivotal studies PALISADE and ARTEMIS. Both studies recruited subjects with a documented history of peanut allergy. Subjects with a severe or life-threatening anaphylaxis event within 60 days of study entry and those with severe or uncontrolled asthma were excluded from the studies. 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 to 40 weeks starting at 3 mg until the 300 mg dose was reached. The Up-Dosing period varied for each subject depending on doses tolerated. Subjects then underwent 6 months (PALISADE) or 3 months (ARTEMIS) of maintenance immunotherapy with 300 mg PALFORZIA or placebo until the end of the study when subjects completed an exit DBPCFC to assess desensitisation to peanut.

PALISADE recruited subjects aged 4 to 55 years in Europe and North America. A total of 750 subjects aged 4 to 17 years were screened and 499 were randomly assigned (3:1) to study treatment (374 to PALFORZIA and 125 to placebo). The primary efficacy analysis population consisted of 496 subjects aged 4 to 17 years who received at least one dose of study treatment. In this study, eligible subjects were those sensitive to $\leq$ 100 mg of peanut protein at the screening DBPCFC. Of the subjects treated with PALFORZIA in the primary analysis population, 72% had a medical history of allergic rhinitis, 66% reported multiple food allergies, 63% had a medical history of atopic dermatitis, and 53% had a present or previous diagnosis of

asthma. The median age of subjects was 9 years. More than half of the subjects were male (56%) and most subjects were white (78%).

ARTEMIS recruited subjects aged 4 to 17 years of age in Europe. A total of 175 subjects aged 4 to 17 years were randomly assigned (3:1) to study treatment (132 to PALFORZIA and 43 to placebo). The primary efficacy analysis population consisted of 175 subjects aged 4 to 17 years who received at least one dose of study treatment. In this study, eligible subjects were those sensitive to ≤ 300 mg of peanut protein at the screening DBPCFC. Of the subjects treated with PALFORZIA in the primary analysis group, 61% reported multiple food allergies, 59% had a medical history of atopic dermatitis, 48% had a medical history of allergic rhinitis, and 42% had a present or previous diagnosis of asthma. The median age of subjects was 8.0 years. More than half of the subjects were male (52%) and most subjects were white (82%).

Efficacy data

The primary efficacy endpoint in both PALISADE and ARTEMIS was the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 1,000 mg peanut protein with no more than mild allergic symptoms at the exit DBPCFC (desensitisation response rate). Key secondary endpoints in this age group included determination of the desensitisation response rates after single doses of 300 mg and 600 mg peanut protein and the maximum severity of symptoms at the exit DBPCFC.

Desensitisation response rates

The summary of desensitisation response rates for primary and secondary efficacy endpoints for the intention to treat (ITT) population in both PALISADE and ARTEMIS are provided in Table 9. Subjects without an exit DBPCFC were counted as non-responders.

Table 9: PALISADE and ARTEMIS: Summary of desensitisation response rates for primary and key secondary efficacy endpoints (ITT population, 4-17 years)

Endpoint	PALISADE		ARTEMIS	
	PALFORZIA N = 372	**Placebo N = 124**	**PALFORZIA N = 132**	**Placebo N = 43**
Primary efficacy endpoint				
Response rate: proportion of subjects who tolerated 1,000 mg peanut protein (95% CI) [1]	50.3% (45.2, 55.3)	2.4% (0.8, 6.9)	58.3% (49.4, 66.8)	2.3% (0.1, 12.3)
P-value [2]	< 0.0001		< 0.0001	
Key secondary efficacy endpoints				
Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI) [1]	67.2% (62.3, 71.8)	4.0% (1.7, 9.1)	68.2% (59.5, 76.0)	9.3% (2.6, 22.1)
P-value [2]	< 0.0001		< 0.0001	
Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI) [1]	76.6% (72.1, 80.6)	8.1% (4.4, 14.2)	73.5% (65.1, 80.8)	16.3% (6.8, 30.7)
P-value [2]	< 0.0001		< 0.0001	

[1] PALISADE: Based on Wilson (score) confidence limits, ARTEMIS: Based on exact Clopper-Pearson interval.

[2] PALISADE: Based on the Farrington-Manning confidence limits. ARTEMIS: Based on exact unconditional confidence limits using the score statistic; p-values were based on Fisher's exact test.

CI, confidence interval.

Response rates in subjects who turned 18 years during therapy

The response rate of PALFORZIA treated subjects who turned 18 years whilst participating in a study and tolerated a single highest dose of at least 1,000 mg peanut protein with no more than mild allergic symptoms at the exit DBPCFC (15/27, 55.6%) was consistent with the overall primary efficacy of the subjects aged 4 to 17 years.

Sustained efficacy

Sustained efficacy has been demonstrated in 104 subjects and 26 subjects who completed 12 and 18 months of PALFORZIA maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both PALISADE and the open-label, follow-on ARC004 study. A comparison of response rates after longer-term maintenance therapy with PALFORZIA can be made by comparing the response rates for the 12-month and 18-month maintenance cohorts in ARC004 with those who completed PALISADE (see Table 10).

Table 10: Percentage of challenge doses tolerated following continued maintenance during exit DBPCFC (PALISADE and ARC004 completer populations, 4-17 years)

	PALISADE	ARC004	
	6-month maintenance (N = 296)	12-month maintenance (N = 104)	18-month maintenance (N = 26)
Subjects who tolerated a single dose of peanut protein (response rate) [95% CI]			
2,000 mg	na [1]	50 (48.1%) [38.2%, 58.1%]	21 (80.8%) [60.6%, 93.4%]
1,000 mg	187 (63.2%) [57.5%, 68.5%]	83 (79.8%) [70.8%, 87.0%]	25 (96.2%) [80.4%, 99.9%]
600 mg	250 (84.5%) [79.9%, 88.1%]	93 (89.4%) [81.9%, 94.6%]	25 (96.2%) [80.4%, 99.9%]
300 mg	285 (96.3%) [93.5%, 97.9%]	102 (98.1%) [93.2%, 99.8%]	26 (100%) [86.8%, 100.0%]

[1] 1,000 mg was the highest challenge dose of peanut protein in PALISADE.
DBPCFC, double-blind, placebo-controlled food challenge; CI confidence interval; na, not applicable.

5.2 Pharmacokinetic properties

No clinical studies investigating the pharmacokinetic profile and metabolism of PALFORZIA have been conducted. PALFORZIA contains naturally occurring allergenic peanut proteins. After oral administration, the proteins are hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract.

5.3 Preclinical safety data

Non-clinical studies with defatted powder of *Arachis hypogaea L.*, semen (peanuts) have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PALFORZIA 300 mg oral powder in sachet

Microcrystalline cellulose

Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years – Initial dose escalation pack

3 years – All packs except initial dose escalation pack

After mixing a daily dose of PALFORZIA with age-appropriate soft-food, the entire volume of the prepared mixture should be consumed promptly, but if necessary, can be refrigerated for up to 8 hours.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Initial dose escalation phase (see section 4.2)

Initial dose escalation pack

PVC:PCTFE/Aluminium blister containing 13 capsules (2 x 0.5 mg + 11 x 1 mg) in 5 single-dose blisters.

Up-dosing phase (see section 4.2)

Each 2-week pack contains additional doses in case of need.

Name/Capsule or Sachet strength	**Pack contents by dose level (daily dose)**
PALFORZIA 1 mg oral powder in capsules for opening	**Level 1 (3 mg daily):** 48 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains three 1 mg capsules **Level 2 (6 mg daily):** 96 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains six 1 mg capsules
PALFORZIA 10 mg PALFORZIA 1 mg oral powder in capsules for opening	**Level 3 (12 mg daily):** 48 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains one 10 mg capsule and two 1 mg capsules
PALFORZIA 20 mg oral powder in capsules for opening	**Level 4 (20 mg daily):** 16 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains one 20 mg capsule **Level 5 (40 mg daily):** 32 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains two 20 mg capsules **Level 6 (80 mg daily):** 64 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains four 20 mg capsules
PALFORZIA 100 mg oral powder in capsules for opening	**Level 9 (200 mg daily):** 32 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains two 100 mg capsules

Name/Capsule or Sachet strength	**Pack contents by dose level (daily dose)**
PALFORZIA 100 mg PALFORZIA 20 mg oral powder in capsules for opening	**Level 7 (120 mg daily):** 32 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains one 100 mg capsule and one 20 mg capsule **Level 8 (160 mg daily):** 64 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains one 100 mg capsule and three 20 mg capsules **Level 10 (240 mg daily)**: 64 capsules in PVC:PCTFE/Aluminium blisters in a carton Each blister-well contains two 100 mg capsules and two 20 mg capsules
PALFORZIA 300 mg oral powder in sachet	**Level 11 (300 mg daily):** 15 PET/Aluminium/mLLDPE foil sachets in a carton

Maintenance phase (see section 4.2)

Maintenance pack:

Each pack of PALFORZIA 300 mg oral powder contains
30 PET/Aluminium/mLLDPE foil sachets in a carton.

6.6 Special precautions for disposal

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Unused medicinal product or waste material includes opened capsule(s) (i.e., empty or contained powder that was not used) or sachet(s), and prepared mixtures not consumed within 8 hours.

7 MARKETING AUTHORISATION HOLDER

STALLERGENES
6 rue Alexis de Tocqueville
92160 Antony
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04534/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/09/2024