EU Risk Management Plan
for
PALFORZIA

(Defatted powder of *Arachis hypogaea L.*, semen (peanuts))

RMP version to be assessed as part of this application:	
RMP Version number:	1.2
Data lock point for this RMP:	30 January 2024
Date of final sign off:	21 March 2024
Rationale for submitting an updated RMP:	To update the indication for PALFORZIA to include the treatment of patients 1 to 3 years with a confirmed diagnosis of peanut allergy.
Summary of significant changes in this RMP:	To update the posology guidance for PALFORZIA treatment. To update the clinical trial exposure for studies ARC003, ARC004, ARC007, ARC011, ARC001, ARC002, ARC008, and ARC010 (combined). To update the clinical trial exclusion criteria for study ARC005 with updated SmPC contraindications and warnings. To update the clinical trial ethnicity exposure data for special populations. To update the post-authorisation exposure data up to 30 January 2024. To update the important identified risks with data from the updated integrated safety population, study ARC008, study ARC005, and post-marketing cases up to 30 January 2024. To update the study milestones for study ARC008.

	To update the specific parents/caregivers educational materials for patients aged 4 to 6 years old to cover patients 1 to 6 years old. To update the Summary of the RMP and Annexes (Annexes 6 and 8) in line with the updates made to the RMP.
Other RMP versions under evaluation:	
RMP Version number:	Not applicable
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Details of the currently approved RMP:	
RMP Version number:	1.0
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EU QPPV name: Katia DAGHILDJIAN

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

ACE	Angiotensin-converting enzyme
AIT	Allergen immunotherapy
Ara h 1, Ara h 2, Ara h 6	Peanut allergens
ARB	Angiotensin-receptor blocker
ASA	Acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CP	Centralised procedure
CSR	Clinical study report
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EEA	European Economic Area
EGD	Esophagogastroduodenoscopy
EMA	European Medicines Agency
EoE	Eosinophilic oesophagitis
EPAR	European Public Assessment Report
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FLG	Filaggrin
FPIES	Food protein-induced enterocolitis syndrome
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HPMC	Hydroxypropyl methyl cellulose
IBD	International birth date
ICS	Inhaled corticosteroid

IDE	Initial Dose Escalation
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL-5	Interleukin-5
IL-13	Interleukin-13
IM	Intramuscular
IND	Investigational New Drug
INN	International Non-proprietary Name
ITIM	Immunoreceptor tyrosine based inhibitory motif
IV	Intravenous
LABA	Long-acting β-2 agonist
LEAP	Learning Early About Peanut Allergy
LLT	Lower Level Term
LTRA	Leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NPP	Named-patient product
NSAID	Non-steroidal anti-inflammatory drug
OFC	Oral food challenge
OIT	Oral immunotherapy
OLFC	Open-label food challenge
OR	Odds ratio
PAL	Precautionary allergen labelling
PDCO	Paediatric Committee
PIP	Paediatric investigation plan
PL	Package leaflet
POSEIDON	Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (ARC005)

PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
ps-IgE	Peanut-specific immunoglobulin E
ps-IgG4	Peanut-specific immunoglobulin G4
QoL	Quality of life
QPPV	Qualified person responsible for pharmacovigilance
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk management plan
SABA	short-acting β-2 agonist
SCIT	Subcutaneous immunotherapy
sIgE	Specific IgE
SLIT	Sublingual immunotherapy
SmPC	Summary of product characteristics
SOC	System organ class
SPT	Skin prick test
Th2	Type 2 helper T lymphocyte
UK	United Kingdom
US	United States of America
UV	Ultraviolet
WHO	World Health Organization

Part I: Product Overview

Table 1: Product Overview

Active substance (INN or common name)	Defatted powder of *Arachis hypogaea* L., semen (peanuts)
Pharmacotherapeutic group (ATC Code)	Allergen, allergen extracts (V01AA08)
Marketing Authorisation Holder	Stallergenes Greer
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	PALFORZIA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Plant allergen
	Summary of mode of action: The precise mechanism of desensitization provided by defatted powder of *Arachis hypogaea L.*, semen (peanuts) is not fully understood.
	Important information about its composition: PALFORZIA capsules and sachets contain defatted powder of *Arachis hypogaea L.*, semen (peanuts). PALFORZIA does not contain animal-derived or sourced materials. PALFORZIA 0.5 mg, 1 mg, 10 mg, and 20 mg oral powder contains partially pre-gelatinised maize starch.
Hyperlink to the Product Information	PALFORZIA product information (Module 1.3.1)
Indication in the EEA	Current: 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.
	Proposed: PALFORZIA is indicated for the treatment of patients aged 1 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.
Dosage in the EEA	Current: 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. 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 of 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.

Table2: 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.

Proposed:

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.

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 treatment 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 3 mg for patients 1 to 3 years and with 6 mg for patients 4 to 17 years (see Table 1 and 2).

Table 1: Dose and capsule presentation for initial dose escalation for patients 1 to 3 years old

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

Table 2: Dose and capsule presentation for initial dose escalation for patients 4 to 17 years old

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 x 1 mg capsules

The same initial dose escalation pack is used for patients aged 1 to 3 years old and for patients 4 to 17 years old.

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 1 mg single dose (ages 1 to 3 years) and the 3 mg single dose (ages 4 to 17 years) of 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.

Patients 1 to 3 years old

Up-dosing consists of 12 dose levels and is initiated at a 1 mg dose (Level 0) and up-dosed to Level 11 (see Table 3).

Patients 4 to 17 years old

Up-dosing consists of 11 dose levels and is initiated at a 3 mg dose (Level 1) and up-dosed to Level 11 (see Table 4).

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 Tables 3 and 4 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 Tables 3 and 4.

Table 3: Daily dosing configuration for up-dosing in patients 1 to 3 years old

Dose level	Total daily dose	Presentation of dose (capsule colour)	Dose duration (weeks)
0	1 mg	1 x 1 mg capsule (red)	2
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

Table 4: Daily dosing configuration for up-dosing in patients 4 to 17 years old

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 Tables 3 and 4 (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 5: 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 for ages 4 to 17 years. No recommendation can be made about the duration of treatment beyond 24 months.

Efficacy data currently are available for up to 12 months of treatment with PALFORZIA for ages 1 to 3 years. No recommendation can be made about the duration of treatment beyond 12 months.

Stopping treatment will likely not maintain achieved efficacy. If treatment with PALFORZIA is stopped, patients must continue to carry self-injectable adrenaline at all times.

Pharmaceutical form and strengths

Current: White to beige oral powder in capsules for opening or sachet. PALFORZIA oral powder is available in capsules for opening of 0.5 mg, 1 mg, 10 mg, 20 mg, 100 mg dosage strengths, and a sachet of 300 mg dosage strength.

PALFORZIA 0.5 mg oral powder in capsules for opening

	Oral powder in white opaque hard capsules (16 x 6 mm) PALFORZIA 1 mg oral powder in capsules for opening Oral powder in red opaque hard capsules (16 x 6 mm) PALFORZIA 10 mg oral powder in capsules for opening Oral powder in blue opaque hard capsules (23 x 9 mm) PALFORZIA 20 mg oral powder in capsules for opening Oral powder in white opaque hard capsules (23 x 9 mm) PALFORZIA 100 mg oral powder in capsules for opening Oral powder in red opaque hard capsules (23 x 9 mm) PALFORZIA 300 mg oral powder in sachet Oral powder
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population

Indication

PALFORZIA is indicated for the treatment of patients aged 1 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.

Peanut allergy is a common and potentially serious condition that disproportionately affects children and is associated with severe allergic reactions, including life-threatening anaphylaxis. Peanut and tree nut allergies account for most fatal food-induced anaphylaxis (Sampson, 2005).

The major allergens to foods are defined by those that bind to IgE in greater than 50% of the allergic population. The major peanut allergens are Ara h 1 and Ara h 3, which are members of the cupin superfamily of proteins, and Ara h 2 and Ara h 6, which are members of the prolamin superfamily (Mueller, 2014). These allergens can trigger an Immunoglobulin E (IgE)-mediated immune response via release or generation of mast cell- or basophil-derived inflammatory mediators (Mueller, 2014).

Despite efforts at strict peanut avoidance, accidental exposure remains a major concern because allergic responses may be triggered by minute quantities (milligrams) of peanut protein. Strict adherence to an avoidance diet can be complicated by difficulty in interpreting food labels (Joshi, 2002), the presence of undeclared or inadvertent introduction of allergens in commercially-prepared foods (Vierk, 2002; Altschul, 2001), and inattention to or mistrust of food warning labels (Vierk, 2007). Foods prepared outside the home (eg, at school, day-care centres, restaurants, homes of family/friends) present additional sources of accidental exposure. Allergen-specific immunotherapy is an approach that has shown consistent and promising results. Increasing amounts of an allergen are administered to patients with IgE-mediated food allergy to raise the reactivity threshold and decrease the severity of allergic responses to the allergenic food. Oral immunotherapy (OIT) is the most widely studied route of administration for food allergen immunotherapy (Pajno, 2017).

The MAH developed PALFORZIA using a characterized OIT desensitization approach for patients with peanut allergy. PALFORZIA, characterized peanut (*Arachis hypogaea*) allergens, is used in a regimented OIT protocol to reduce the incidence and severity of allergic reactions, including anaphylaxis, in an individual with peanut allergy after unintended exposure to peanut.

Prevalence and incidence:

Peanut allergy is a potentially life-threatening disease that disproportionately affects children, resolving in only approximately 20% of affected individuals (Skolnick, 2001). In Europe, the prevalence of peanut allergy in children is approximately 1.6% as estimated by food challenges or clinical history (Nwaru, 2014). In adolescents and adults in the UK, the self-reported prevalence of peanut allergy was 0.53% for 15- to 44-year-olds and 0.3% > 45-year-olds (Stiefel, 2017).

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia (Du Toit, 2015). In the

US in 1999 peanut allergy was estimated to affect 0.4% of children and 0.7% of adults (Sicherer, 1999) and by 2010, peanut allergy prevalence had increased to approximately 2% among children in a national survey (Gupta, 2011). In another US study the prevalence of peanut allergy in children was 1.4% (95% confidence interval [CI], 1.0%–1.9%) in 2008 compared with 0.8% in 2002 (P = not significant) and 0.4% in 1997 (P < 0.0001) (Sicherer, 2010).

Demographics of the population in the proposed indication – age, sex, racial and/or ethnic origin and risk factors for the disease:

Peanut allergy has a greater prevalence in young children than in adults. In 2008 the prevalence of peanut allergy in preschool and school-age children was approximately 1.2% to 1.6%, whereas the prevalence in US adults was estimated to be 0.6% (Sicherer, 2010). In those under 18 years of age, the crude lifetime prevalence rate is higher in males than females (Kotz, 2011).

Peanut allergy is strongly heritable, with concordance rates of 64% for monozygotic twins compared with 7% for dizygotic twins (Sicherer, 2000) and other siblings. The prevalence of peanut allergy in siblings of children with peanut allergy is 5%–9% (Stiefel, 2017). In a UK questionnaire survey the prevalence of peanut allergy in siblings of people with peanut allergy was 6.9% and found to be more common than in the parents (1.6%) or the general population (1.3%) (Hourihane, 1996). A 2005–2006 survey of 560 Canadian households of children born in 1995 identified 4 of 47 (8.5%) siblings of peanut-allergic children and 11 of 853 (1.3%) siblings of non-peanut-allergic children to have peanut allergy, with the risk of peanut allergy markedly increased in siblings of a peanut-allergic child (odds ratio [OR] 6.72, 95% CI, 2.04-22.12) (Liem, 2008).

National differences in the risk of peanut allergy in children living in different countries have been reported. The risk of peanut allergy was found to be 10 times higher among Jewish children in the UK (prevalence of 1.85%) as it was in Israeli children (prevalence of 0.17%) of similar ancestry (P < 0.001) (Du Toit, 2008). In this study the adjusted risk ratio for peanut allergy between countries was 9.8 (95% CI, 3.1–30.5) in primary school children. A nested case-control analysis of 159 of the UK children (103 without food allergy and 56 with food allergy) showed no effect of Sephardic, Ashkenazi, or mixed background on food allergy.

Importantly this difference was not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity, but the observation correlated with the time at which peanuts were introduced in the diet in these countries (Du Toit, 2008). The UK infants typically did not consume peanut-based foods in the first year of life, whereas in Israel, peanut-based foods were usually introduced in the diet when infants were approximately 7 months of age, and their median monthly consumption of peanut protein was 7.1 g (Du Toit, 2008). At the time of this publication, dietary avoidance of peanut during pregnancy, breastfeeding, and early life had been recommended in the UK and Australia and in the US. However, studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to prevent IgE-mediated food allergy (Zeiger, 1995). This finding led Du Toit et al to hypothesize that the early introduction of peanuts to the diet may offer protection from the development of peanut allergy, and this hypothesis was tested in the Learning Early About Peanut Allergy (LEAP) trial described below (Du Toit, 2015).

Peanut allergy is often associated with other atopic diseases. The allergic march refers to the natural history of atopic disorders and concerns the development of atopic dermatitis and concomitant sensitisation to food and aeroallergens in early childhood, progressing to asthma and allergic rhinitis in later childhood or adult life (Thomsen, 2015). Atopic diseases frequently accompany or precede asthma, and about 40% of all children with asthma have a history atopic

dermatitis (Lowe, 2008). Importantly up to 50% of peanut-allergic individuals have asthma (Clark, 2008). Infants with severe eczema and/or egg allergy also have a higher risk of developing peanut allergy (Stiefel, 2017).

Early-life environmental peanut exposure is associated with an increased risk of peanut sensitisation and allergy in children who carry a filaggrin (FLG) mutation (Brough, 2015). Mutations in FLG, a gene that encodes a skin barrier protein, are a novel risk factor for IgE-mediated peanut allergy, indicating a role for epithelial barrier dysfunction in the pathogenesis of the disease (Asai, 2013; Brown, 2011). FLG mutation carriers have a greatly increased risk of common complex traits, including atopic dermatitis (which affects 42% of all mutation carriers), contact allergy, asthma, hay fever, sensitisation, atopic eczema, allergic rhinitis and peanut allergy (van den Oord, 2009; Irvine, 2011). These genetic variants also influence the severity of asthma and alopecia areata and susceptibility to herpetic infection (Asai, 2013). FLG plays a role in skin barrier formation and eczema, and eczema is a significant risk factor for primary nut allergy (Stiefel, 2017). It has been hypothesised that allergic sensitisation in the atopic state occurs via either transcutaneous or transmucosal passage of allergens, a process that may be facilitated by FLG deficiency (Leung 2009; Brown, 2011) and that peanut allergy may develop through transcutaneous sensitisation in children with an impaired skin barrier function such as eczema (dual-allergen hypothesis) (Lack, 2008). The discovery of FLG gene mutations as a predisposing factor for atopic dermatitis and subsequent asthma and sensitisation in the context of eczema means that the atopic diseases can be viewed as causally related conditions rather than sequentially occurring manifestations of the same underlying disease state (Thomsen, 2015).

The main existing treatment options:

The prevention and current management of peanut allergy are described below.

Prevention

Historically clinical practice guidelines from the UK in 1998 (COT, 1998) and from the US in 2000 (American Academy of Pediatrics, 2000) recommended the exclusion of allergenic foods from the diets of infants at high risk for allergy and from the diets of their mothers during pregnancy and lactation in an effort to prevent the development of food allergies. However, recommendations for dietary avoidance of peanut during pregnancy, breastfeeding, and in early life as previously recommended in the UK, Australia and in the US (Du Toit, 2008), are now changing with scientific advances. Current recommendations include the introduction of peanut-containing products into the diets of "high-risk" infants (defined as having egg allergy or atopic dermatitis) early in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent because delaying the introduction of peanut can be associated with an increased risk of peanut allergy (Fleischer, 2015).

The LEAP study, a randomised, open-label, controlled trial, was conducted to determine whether the early introduction of dietary peanut could serve as an effective primary and secondary strategy for the prevention of peanut allergy (Du Toit, 2015). The LEAP trial randomised 640 children between 4 and 11 months of age with severe eczema, egg allergy, or both to consume (at least 6 g of peanut protein per week) or avoid peanut-containing foods until 60 months of age, at which time a peanut oral food challenge (OFC) was conducted to determine the prevalence of peanut allergy (Du Toit, 2015). Among the 530 infants with high-risk atopic disease in the intention-to-treat population, peanut consumption was associated with an 86% reduction in peanut allergy at 60 months of age among participants who had had negative results on a peanut-based skin prick test

(SPT) at study entry and with a 70% reduction among those who had had positive test results at study entry.

A 12-month extension of the LEAP study, the LEAP-on study, investigated whether participants who consumed peanut remain protected against peanut allergy, even after cessation of peanut consumption for 12 months (Du Toit, 2016). The reduction in peanut allergy achieved through early peanut introduction and consumption (until 60 months of age) was found to persist at 72 months of age, even after 12 months of peanut avoidance. There was a 74% relative reduction in the prevalence of peanut allergy in the previous LEAP consumers compared with the previous LEAP avoiders, demonstrating longer-lasting unresponsiveness to peanut after 12 months of peanut avoidance. Immunologic findings (small SPT wheal size, continued decrease in Ara h 2 specific IgE (sIgE) levels, and high peanut-specific immunoglobulin G4 [IgG4]/IgE ratios) noted in non-allergic LEAP consumers at month 60 were maintained after 12 months of peanut avoidance (Du Toit, 2016).

The LEAP trial has already influenced national guidelines. Following the LEAP trial and other emerging data suggesting that peanut allergy can be prevented through introduction of peanut-containing foods beginning in infancy, the US National Institute of Allergy and Infectious Diseases (NIAID) along with 25 professional organisations, federal agencies, and patient advocacy groups facilitated development of addendum guidelines to specifically address the prevention of peanut allergy (Togias, 2017). Other Guidelines such as the European Academy of Allergy and Clinical Immunology's (EAACI) guidelines for food allergy and anaphylaxis available on the EAACI website advise that the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity (Muraro, 2014).

Current therapies

Treatment modalities prescribed for patients with peanut allergy aim to prevent exposure to a known food allergen or treat allergic reactions due to accidental exposure. The current standard of care for the management of peanut allergy is peanut avoidance. Patients are required to follow a strict peanut-avoidant diet, which can be difficult and imposes a significant quality of life (QoL) burden (Flokstra-de Blok, 2010), as described below.

Because strict peanut avoidance is difficult, unintended exposures may occur. Accidental exposures are common and cause reactions of unpredictable severity, even with small exposures (Deschildre, 2016; Allen, 2014; Vander Leek, 2000). When these exposures result in allergic symptoms, rescue medications, including antihistamines or epinephrine, may be required for treatment. An important part of management is the education of the patient and family on recognition and management of allergy symptoms with rescue medications (eg, epinephrine auto-injectors).

For those patients who are allergic to peanuts, allergen immunotherapy to desensitise to food allergens has been used. The allergen immunotherapy (AIT) Guidelines Part II prepared by the EAACI Task Force on allergen immunotherapy for IgE-mediated food allergy recommends that allergen immunotherapy should only be performed in research centres or in clinical centres with an extensive experience in food allergy AIT (Pajno, 2017). There are currently no approved products for use for peanut desensitisation. Accordingly, at some clinics unapproved peanut-containing products, known as named-patient products (NPPs) in the EU and subject to different national requirements (Pajno, 2017), are being administered to induce desensitisation in peanut-allergic patients. The unapproved products used for desensitisation are not characterised with respect to their antigen contents nor are they necessarily consistent in terms of quality from

batch to batch. In most cases their dosage regimen has not been evaluated in a clinical trial setting. Therefore, there is an increased risk to patients of anaphylaxis or of inadequate desensitisation.

PALFORZIA was first approved in the US on 31 January 2020 and launched in the US since 04 March 2020.

As of the 30 January 2023, PALFORZIA is authorised and launched in the EU, Switzerland, UK, and US.

In the EU, PALFORZIA was authorised on 17 December 2020 through the centralised procedure (CP) and later launched in Germany (15 October 2021), Austria (13 April 2022), Sweden (02 December 2022) and France (04 January 2023). In the UK, the conversion of the PALFORZIA EU CP to Great Britain Marketing Authorisation was validated by the Medicines and Healthcare products Regulatory Agency (MHRA) on 07 April 2021; PALFORZIA was launched in the UK on 11 October 2021. In Switzerland, PALFORZIA was authorised on 04 May 2021 through a national procedure and launched as of 15 June 2022.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Immediate symptoms of peanut allergy are related to the cross-linking of cell membrane-bound antigen-specific IgE which results in the release histamine and other pro-inflammatory mediator substances from mast cells and basophils (degranulation). In addition to other effects, histamine induces vasodilation of arterioles and constriction of bronchioles in the lungs, also known as bronchospasm. Type 1 (immediate or IgE mediated) hypersensitivity reactions encompass a wide range of symptoms that can manifest in multiple system organ classes (SOCs) such as the respiratory, gastrointestinal (GI), skin, and cardiovascular systems. Symptoms can be localised or involve more than one body system (ie, systemic), and range in severity from mild and self-limiting (eg, pruritis, urticaria) to life-threating (airway obstruction, shock) or fatal in extreme cases.

As discussed above, the allergic march refers to the natural history of atopic disorders (Thomsen, 2015). The child can develop atopic dermatitis in the first months of life accompanied by sensitisation to cow's milk, egg, or peanut. Vomiting, diarrhoea, or anaphylaxis in relation to ingestion of these foods may begin around the age of 6-12 months. This is followed by sensitisation to indoor allergens such as house dust mite, cockroach, and furred pets. Within the first 2 years of life the child may also develop recurrent episodes of wheezing, mostly in conjunction with viral respiratory tract infections (Singh, 2007). After this age wheezing become more frequent and asthma may develop. Later in childhood, allergy to inhalant allergens may develop followed by allergic rhinoconjunctivitis occurs in relation to exposure to grass and tree pollen. At the same time, eczema and sensitisations to food may or may not wane, but cross-reactions to nuts and fresh fruits and vegetables may develop and give rise to oral allergic manifestations. In the teenage years asthma symptoms may disappear or become less pronounced but skin and upper respiratory symptoms may return. In young and middle adulthood, respiratory and skin manifestations are more closely related to occupational exposures, lifestyle, and tobacco smoking, and hand eczema or asthma-chronic obstructive pulmonary disease overlap syndrome may develop in relation to these exposures. In late adulthood, allergic symptoms generally become less frequent and tend to disappear but in some, new-onset allergy or asthma infrequently develops in old age (Gillman, 2012).

In the majority of patients, peanut allergy begins early in life and generally persists as a lifelong problem (Togias, 2017). Resolution of peanut allergy is sometimes seen in young children

(approximately 20%) (Stiefel, 2017). There are limited data on the natural history of peanut allergy to determine which patients become tolerant. In children under 2 years of age diagnosed with peanut allergy, 21% outgrew their allergy (Fleischer, 2003; Ho, 2008). However, the initial peanut allergy diagnosis in these studies was not based on strict criteria such as a positive oral food challenge (Stiefel, 2017). A recent population-based cohort study of 156 infants with challenge-confirmed peanut allergy at 1 year of age found that peanut allergy resolved in 22 of the 103 infants tested at 4 years of age (22%) with repeat oral food challenges (Peters, 2015). A decreasing skin prick test weal size predicted remission, whereas an increase weal size predicted persistence. Another study showed that spontaneous resolution of peanut allergy predominantly occurred by 6 years of age and occurs at a much lower frequency after 10 years of age (Bégin, 2013). Clinical experience suggests that peanut allergy in teenagers and adults rarely resolve (Stiefel, 2017).

Peanut allergy is the leading cause of death related to food-induced anaphylaxis in the US (Bock, 2007) and although overall mortality is low, the fear of life-threatening anaphylactic reactions contributes significantly to the medical and psychosocial burden of disease (Togias, 2017). Accidental food allergen exposures are common, with 55% of peanut-allergic patients experiencing at least 1 allergic reaction over approximately 5 years (Sicherer, 1998). A survey of US households comprising parent-proxy responses for 38,408 children between 2015 and 2016 found that 22.9% of children reported at least 1 peanut allergy-related visit to the Emergency Department within the past year (Gupta, 2018). A systematic review and meta-analysis of fatal food anaphylaxis estimated an incidence of fatal peanut anaphylaxis of 0.73-4.25 per million person-years (Umasunthar, 2013). Over a 20-year period from 1992 to 2012, 69 of 95 fatalities (73%) were attributed to peanuts and tree nuts based on records of hospital admissions and anaphylactic fatalities from national databases in England and Wales (Turner, 2015). Similarly peanuts were the most frequent triggers of severe allergic reactions in children in an anaphylaxis registry of 1,156 severe allergic reactions registered in Germany, Austria and Switzerland (Worm, 2017). In the European Anaphylaxis Registry involving 10 countries severe allergic reactions were caused by food items in 1291 (66%) of 1970 patients (0 to 17 years of age), with peanut found to be an elicitor for anaphylaxis in all age groups (overall n = 325) (Grabenhenrich, 2016).

Factors associated with life-threatening reactions to peanut include prior anaphylaxis to the same food, co-morbidities (including asthma and mastocytosis), concurrent use of certain medications (eg, non-selective beta-blockers and non-steroidal anti-inflammatory drugs [NSAIDs]), acute respiratory illnesses, menstruation, alcohol and exercise (Brough, 2015; Smith, 2015; Turner, 2017b; Varshney, 2009). A history of severe allergic events including anaphylaxis has been identified as a risk factor for fatal events due to food and future severe allergic reactions (Nguyen-Luu, 2012). However, a history of mild reactions is not predictive of mild future reactions with about half of a UK series of food anaphylaxis deaths found to occur in patients with a history of mild reactions (Pumphrey, 2007). Coexisting asthma is more strongly associated with a severe reaction than the severity of previous reactions (Macdougall, 2002). Increased severity of asthma and uncontrolled asthma can increase the risk of anaphylaxis (González-Pérez, 2010). In the MIRABEL survey, an observational peanut allergy study of 785 patients in France, Belgium and Luxemburg, severe/potentially severe reactions were reported in 30% of the allergic patients (median age 3 years, 85% declared allergic) including serious systemic reaction (15%), laryngeal angioedema (8%), shock (4%) and acute asthma (3%); 66% had atopic dermatitis, 58% asthma (Deschildre, 2016).

Older patients are also susceptible to severe allergic reactions. The age of the patient is an important factor predicting the severity of allergic reactions, with adults 2 to 9 times more likely to

develop severe reactions than children (Summers, 2008). The majority of severe non-fatal and fatal accidental reactions occur in teenagers and young adults (Pumphrey, 2007; Turner, 2015; Turner, 2017b). Several factors are thought to be involved. These include risk-taking behaviour such as failure to avoid triggers, failure to carry an epinephrine autoinjector and use of alcohol (Simons, 2011).

The majority of fatal reactions occur outside the home environment, following exposure to allergens in non-pre-packed food items such as those sold in restaurants. A review of fatal food-triggered anaphylaxis where the source of the food was identified in 100 cases, found that 27 (27%) were caused by the consumption of the allergen in pre-packaged foods and 59 (59%) reactions were to food products provided by a catering establishment, of which one quarter were purchased from takeaway outlets (Turner, 2015).

The burden of avoidance and constant anxiety of accidental exposure can negatively affect the health-related QoL for patients with peanut allergy and their families (Anagnostou, 2014; Avery, 2003; Primeau, 2000; Flokstra-de Blok, 2010; Papadopoulos, 2018; Deschildre, 2016). In the MIRABEL survey consumption of food products by peanut-allergic patients, including those with precautionary allergen labelling (PAL), was found to be modulated by factors related to anxiety such as label reading and knowledge of threshold, with anxiety significantly associated with strict avoidance ($P < 0.001$) (Papadopoulos, 2018; Deschildre, 2016).

Quality of life of affected patients and their families is decreased because of the need for constant vigilance over food choices and the perceived likelihood of anaphylaxis, alongside the dietary and social restrictions that accompany food allergy (Stiefel, 2017; King, 2009). Children with peanut allergy perceive a higher risk (fear of an adverse event and more anxiety about eating, especially when eating away from home) than children with diabetes based on two disease specific QoL questionnaires, with 85% of peanut allergic children reporting the need for constant care regarding the food they ate compared with 50% of diabetic children (Avery, 2003), suggesting an overall worse health-related QoL for peanut allergy than diabetes. Children with peanut allergy were found to have significantly poorer physical health related QoL ($p < 0.05$), QoL within school ($p < 0.01$) and general QoL ($p < 0.05$) than their siblings did and greater separation anxiety ($p < 0.05$) (King, 2009). In the same study mothers rated their own psychological ($p < 0.01$) and physical ($p < 0.05$) QoL significantly worse than fathers rated theirs, and had higher scores than the fathers for anxiety ($p < 0.05$) and stress ($p < 0.001$).

Important co-morbidities and co-medications:

Co-morbidities

Atopic diseases often co-exist including asthma, eczema, allergic rhinitis, and food allergy (Thomsen, 2015; Foong, 2017). As described above, FLG mutation carriers have a greatly increased risk of atopic dermatitis, contact allergy, asthma, hay fever, sensitisation, atopic eczema, allergic rhinitis and peanut allergy (van den Oord, 2009; Irvine, 2011). Children with a peanut or tree nut allergy have a significantly increased risk of allergy to nuts (Stiefel, 2017). Asthma is a recognised co-morbidity in peanut allergic patients, with up to 50% of peanut-allergic individuals having asthma (Clark, 2008). Detection and management of allergic co-morbidities, particularly active management of asthma, are especially important, because of the association between poor asthma control and severe allergic reactions. Patients with a severe history of asthma are at greater risk of life-threatening bronchospasm occurring after ingestion of peanuts and tree nuts

($p < 0.0001$) compared with those without asthma (Summers, 2008). Infants with severe eczema and/or egg allergy also have a higher risk of developing peanut allergy (Stiefel, 2017).

There is evidence that food allergy is associated with increased stress and anxiety in children and an impaired QoL, even compared to other chronic conditions such as diabetes (Stiefel, 2017; Avery, 2003). This is related to constant fear of a severe/fatal allergic reaction when eating, the burden of constant vigilance when making food choices and the resulting social restrictions. For adolescents with food allergy, the measures to avoid allergens, as well as the actual allergic reactions, negatively impact QoL (Cummings, 2010; Marklund, 2007). Adolescents experience a burden of responsibility which negatively impacts their lives with increased stress levels often in the home environment and depression that often persists into adolescence and young adulthood (King, 2009; Ferro, 2016).

Co-medications

Co-medications in patients with peanut allergies are used to treat the co-morbidities and psychological disorders associated with the condition. People with food allergies tend to have other allergic conditions, including eczema, asthma, and multiple allergies. These patients are, therefore, frequently on medications to treat these conditions.

The recommended treatment for children and young people aged 5 to 16 years with asthma include a short-acting β-2 agonist (SABA), an inhaled corticosteroid, a leukotriene receptor antagonist (LTRA) as maintenance therapy and in some patients if asthma is uncontrolled a long-acting β-2 agonist (LABA) in combination with inhaled steroids (NICE, 2017).

Allergen immunotherapy (AIT) may be used for other co-existing allergic conditions such as allergic asthma and allergic rhinitis. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) may be used for mild and moderate allergic asthma, or for treatment of certain aeroallergens.

The recommended first-line treatment for eczema focuses on hydrating topical treatment. Anti-inflammatory treatments based on topical corticosteroids and topical calcineurin inhibitors such as tacrolimus and pimecrolimus are used for exacerbation management; systemic immune-suppressive treatment is an option for severe refractory cases; adjuvant therapy includes ultraviolet (UV) irradiation; dietary recommendations should be given only in diagnosed individual food allergy; and allergen-specific immunotherapy to aeroallergens may be useful in selected cases (Ring, 2012). Dupilumab is more recently approved for treatment of eczema.

Many of these patients use antihistamine for treatment of allergic symptoms including rhinitis and urticaria. Co-medications can also be used as prophylactic treatment such as use of antihistamines to enhance efficacy of specific-allergen immunotherapy and reduce systemic allergic reactions (Müller, 2001).

Concomitant medications used to treat psychological conditions such as anxiety and depression include tricyclic antidepressants and monoamine oxidase inhibitors and are therefore not unexpected in the peanut allergic population.

Part II: Module SII - Non-clinical part of the safety specification

PALFORZIA has not been tested in animals to date as PALFORZIA contains naturally occurring allergenic peanut proteins. Therefore, no safety concerns based on non-clinical findings are available and applicable for human use.

Part II: Module SIII - Clinical trial exposure

As of 30 January 2024, the PALFORZIA clinical development programme in peanut-allergic children and adults consisted of two phase 2 studies (ARC001 and ARC002), and seven phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC010, ARC011, and ARC005). Study conduct is complete for the phase 2 study ARC001 in children and young adults and for its follow-on study ARC002 (conducted to gather additional information on the safety and efficacy of PALFORZIA).

There are four completed, randomised, double-blind, placebo-controlled, phase 3 studies. These include pivotal phase 3 study ARC003, an international study of the efficacy and safety of PALFORZIA in children and adults; pivotal phase 3 study ARC010, a European study of the efficacy and safety of PALFORZIA in children and adolescents; a double-blind, placebo-controlled, real-world safety study ARC007 in children conducted in North America; and randomised, double-blind, placebo-controlled, phase 3 study ARC005 in children aged 1 to 3 years conducted in Europe and North America.

Enrolment and study conduct are complete for ARC004, a follow-on study of ARC003 that explores daily and nondaily dosing interval regimens during Extended Maintenance with PALFORZIA.

Enrolment and study conduct are complete for study ARC011, an open-label, safety extension study comprising PALFORZIA-treated subjects who completed ARC007.

ARC008 is an ongoing, international, open-label, longer-term study for subjects from ARC002, ARC004, ARC005, ARC007, ARC010, and ARC011 to evaluate patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation. ARC008 is complete but as the Clinical Study Report (CSR) is currently under preparation it is still considered an ongoing study.

Exposure data in patients 4 years and older treated with PALFORZIA from studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 are presented in Table 2 to Table 6.

Table 2: Duration of PALFORZIA exposure in patients 4 years and older treated with PALFORZIA in studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 (combined)

Cumulative for all indications (person-time)		
Duration of exposure	**Patients**	**Person-time (years)**
Overall	1258	3023.255

Source: AR101/PALFORZIA ISS RMP Table 1 (t-durexp4.sas)

Table 3: Age group and sex of patients 4 years and older treated with PALFORZIA in studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 (combined)

Age group	Patients		Person-time (years)	
4–11 years	814		2135.091	
12–17 years	388		780.539	
18–55 years	56		107.625	
Total	1258		3023.255	
Sex	**Patients**		**Person-time (Years)**	
	M	**F**	**M**	**F**
	759	499	1848.435	1174.820
Overall	1258		3023.255	

Source: AR101/PALFORZIA ISS RMP Table 2 (t-agesex4.sas)

Table 4: Dose of PALFORZIA in patients 4 years and older treated with PALFORZIA in studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 (combined)

Dose of exposure	Patients	Person-time (years)
Initial escalation	1258	7.893
Up-dosing	1230	525.467
Maintenance + extended maintenance	1038	2415.808
Overall	1258	2969.046

Source: AR101/PALFORZIA ISS RMP Table 3 (t-dose4.sas)

Table 5: Ethnic origin of patients 4 years and older treated with PALFORZIA in studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 (combined)

Ethnic origin	Patients	Person-time (years)
White	947	2267.603
Not white	295	715.168
Overall	1242	2982.771

Source: AR101/PALFORZIA ISS RMP Table 4 (t-ethnic4.sas)
Note: Subjects with missing or inconsistent race values are excluded from the analysis.

Table 6: Asthmatic and non-asthmatic patients 4 years and older and treated with PALFORZIA in studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, ARC011 (combined)

	Patients	Person-time (years)
Asthmatic	643	1479.225
Non-Asthmatic	615	1544.030
Total	1258	3023.255

Source: AR101/PALFORZIA ISS RMP Table 5 (t-asthm4.sas)

Exposure data in patients aged 1 to 3 years treated with PALFORZIA from study ARC005 are presented in Table 7 to Table 12.

Table 7: Total PALFORZIA exposure in patients aged 1 to 3 years in study ARC005

	Patients (PALFORZIA)	Person-time (years)
Dose of exposure		
Initial dose escalation	98	0.6
Up-dosing	98	51.7
Maintenance	87	46.2
Overall	98	98.4

Source: Table 14.3.1.1
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

Table 8: Duration of PALFORZIA exposure in patients aged 1 to 3 years treated with PALFORZIA in study ARC005

	Patients (N=98)
Duration of exposure (months) [1]	
n	98
Mean (SD)	12.07 (3.715)
Median	12.24
Q1, Q3	11.51, 14.05
Min, Max	0.2, 19.0
Duration of exposure (days) [1]	
n	98
Mean (SD)	366.8 (112.94)
Median	372.0
Q1, Q3	350.0, 427.0

	Patients (N=98)
Min, Max	6, 577
Duration of exposure by category, n (%)	
≤ 28 days	1 (1.0%)
29 - 56 days	2 (2.0%)
57 - 84 days	3 (3.1%)
85 - 112 days	0
113 - 140 days	1 (1.0%)
141 - 168 days	1 (1.0%)
169 - 196 days	1 (1.0%)
197 - 224 days	1 (1.0%)
225 - 252 days	1 (1.0%)
253 - 280 days	3 (3.1%)
281 - 308 days	0
309 - 336 days	1 (1.0%)
337 - 364 days	29 (29.6%)
365 - 392 days	16 (16.3%)
393 - 420 days	11 (11.2%)
421 - 448 days	10 (10.2%)
449 - 476 days	7 (7.1%)
477 - 504 days	1 (1.0%)
505 - 532 days	5 (5.1%)
> 532 days	4 (4.1%)

[1] Duration of exposure to study treatment was calculated as the date of last dose of study product - the date of first dose of study product + 1.
Source: Table 14.3.5.1
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

Table 9: Age group and sex of patients aged 1 to 3 years treated with PALFORZIA in study ARC005

	Patients (N=98)	Person-time (years)
Age group, n (%)		
1 - < 2 years	33 (33.7%)	36.5
2 - < 3 years	35 (35.7%)	33.3
3 - < 4 years	30 (30.6%)	28.6
Sex, n (%)		
Male	57 (58.2%)	56.7
Female	41 (41.8%)	41.7

Source: Table 14.1.3.2; Table ARC005_exp_agegrp; Table ARC005_exp_sex
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

Table 10: Race of patients aged 1 to 3 years treated with PALFORZIA in study ARC005

	Patients (N=98)	Person-time (years)
Race, n (%)[1]		
American Indian or Alaska Native	0	0
Asian	18 (18.4%)	20.9
Black or African American	4 (4.1%)	3.1
Native Hawaiian or Other Pacific Islander	0	0
White	66 (67.3%)	64.7
Other	8 (8.2%)	8.0
Not collected	4 (4.1%)	3.8

Source: Table 14.1.3.2; Table ARC005_exp_race
[1] Subjects could be included in more than 1 category.
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

Table 11: Ethnicity of patients aged 1 to 3 years treated with PALFORZIA in study ARC005

	Patients (N=98)	Person-time (years)
Ethnicity, n (%)		
Hispanic or Latino	5 (5.1%)	5.2
Not Hispanic or Latino	75 (76.5%)	74.9
Not collected	18 (18.4%)	18.4

Source: Table 14.1.3.2; Table ARC005_exp_eth
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

Table 12: Asthmatic and non-asthmatic patients aged 1 to 3 years treated with PALFORZIA in study ARC005

	Patients (N=98)	Person-time (years)
Asthmatic	10 (10.2%)	9.2
Non-Asthmatic	88 (89.8%)	89.2

Source: Table 14.1.3.2; Table ARC005_exp_asthma
Data cut-off for study ARC005 is 05 July 2022 (Last subject visit).

For the purposes of safety analyses, the controlled population of patients aged 4 to 17 years includes 841 subjects treated with PALFORZIA and 335 subjects treated with placebo from studies ARC003, ARC007, and ARC010.

The integrated safety population is derived from the following 5 clinical studies involving 944 unique subjects aged 4 to 17 years who received at least 1 dose of PALFORZIA:

- Three completed, randomised, double-blind, placebo-controlled, phase 3 studies, ARC003 (Europe and North America), ARC007 (North America only), and ARC010 (Europe only)
- Two uncontrolled, follow-on studies, ARC004 (database lock 15 October 2019) and ARC011 (database lock 12 November 2019)

The data from study ARC008 (database lock 15 December 2018) are currently not amenable to integration and therefore are presented separately from the controlled population and the integrated safety population. Study ARC008 is complete but as the CSR is currently under preparation it is still considered an ongoing study.

As study ARC005 evaluated a different age range of patients (children aged 1 to 3 years) and a different starting dose of PALFORZIA compared with the other studies, the data from ARC005 are presented separately from the controlled population and the integrated safety population.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Key exclusion criteria from the pivotal clinical trials (ARC003, ARC007, and ARC010) are presented below. This is followed by exclusion criteria that are specific to ARC005 that warrant discussion.

Exclusion criteria that are common to the majority of clinical trials are not presented. These criteria include the following: current or recent participation in any other interventional study; pregnancy and lactation; uncertain clinical diagnosis; previous PALFORZIA administration in another clinical trial; history of a chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) at significant risk of becoming unstable or requiring a change in chronic therapeutic regimen; history of alcohol, medication or drug abuse; inability to follow the protocol requirements; and any other condition that, in the opinion of the investigator, precludes participation for reasons of safety.

Other exclusion criteria from ARC003, ARC007, and ARC010 that were designed to ensure that subjects could participate in the trial or to avoid confounding the efficacy and safety results are listed below. Subjects meeting these criteria are not expected to be at higher risk of adverse drug reactions from PALFORZIA than the rest of the indicated population. These include:

- Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing or Double-Blind, Placebo Controlled Food Challenge (DBPCFC)
- Lack of an available palatable vehicle food to which the subject is not allergic
- Use of any therapeutic antibody (eg, omalizumab, mepolizumab, reslizumab), any investigational peanut immunotherapy (eg, oral, sublingual, epicutaneous), or any other immunomodulatory therapy excluding corticosteroids within the past 6 months
- Developing dose limiting symptoms in reaction to the placebo part of the Screening DBPCFC (ARC003 and ARC010)

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension	Medical conditions that reduce the ability to survive a severe allergic reaction or increase the risk of adverse reactions after epinephrine use include unstable angina, recent myocardial infarction, significant arrhythmias, cyanotic congenital heart disease, and uncontrolled hypertension in addition to other conditions as listed in the PALFORZIA product information. Including these patients would have put these	No	Healthcare professionals are advised that PALFORZIA may not be suitable for patients with certain medical conditions described in section 4.4 of the PALFORZIA SmPC. These patients are not appropriate patients for use of PALFORZIA. However, the identification of these patients is based on the medical judgment of the treating healthcare

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
	patients at increased risk and affected the safety evaluation of PALFORZIA in the clinical trials.		professional. Therefore, it is difficult to fully characterize and identify this group of patients.
Use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers, or tricyclic antidepressants	Concomitant use of medicinal products known to inhibit or to potentiate the effect of epinephrine was excluded from the clinical trials to ensure the safety of the patient was not compromised if the use of epinephrine was required. Beta-adrenergic antagonists antagonise the cardiostimulating and bronchodilating effects of epinephrine and alpha-adrenergic antagonists antagonise the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of adrenaline. Patients taking these medications may be unresponsive to the usual doses of epinephrine used to treat systemic allergic reactions, including anaphylaxis. The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants. Other medications that potentiate the effect of epinephrine include levothyroxine sodium, monoamine oxidase inhibitors and certain antihistamines including chlorpheniramine and diphenhydramine. In addition, cardiac glycosides or diuretics may also potentiate the effect of epinephrine and patients taking these medications should be observed carefully for the development of cardiac arrhythmias.	No	The interactions of these medications with epinephrine are well described. These interactions between concomitant medications and the rescue medication are not missing information with respect to PALFORZIA. However, patients on PALFORZIA may need epinephrine during their course of therapy. Concomitant use of medications that potentiate or inhibit effects of adrenaline (epinephrine) is addressed in the warnings and precautions section (section 4.4) of the PALFORZIA SmPC. Healthcare professionals are advised that PALFORZIA may not be suitable for patients who are taking medications that can inhibit or potentiate the effect of epinephrine and to refer to the SmPC for epinephrine for further information.
History of severe or life-threatening episode of anaphylaxis or	These patients were excluded as their inclusion could have confounded the safety or	No	Initiation of treatment with PALFORZIA should be determined by the treating

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
anaphylactic shock within 60 days of Screening	efficacy evaluation of PALFORZIA in the study and to allow the patient time to completely recover from the episode of anaphylaxis. Subjects were admitted to the study if the anaphylaxis happened prior to 60 days before screening.		physician taking the individual circumstances of each patient into account. A 60 day period was considered reasonable to be certain that the prior episode of anaphylaxis was fully resolved. Healthcare professionals are advised in section 4.3 of the PALFORZIA SmPC that PALFORZIA treatment is contraindicated in patients who had severe or life-threatening anaphylaxis within 60 days before initiating treatment with PALFORZIA.
History of eosinophilic oesophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed aetiology	Eosinophilic oesophagitis has been reported in association with oral immunotherapy (Hill, 2017). In order to minimise the risk to patients these patients were excluded from study participation.	No	In clinical practice, use of PALFORZIA in patients with a history of, or current, EoE, other eosinophilic gastrointestinal disease, chronic, recurrent, or severe GERD, or dysphagia is contraindicated. Eosinophilic oesophagitis is an important identified risk of PALFORZIA (Section SVII.3.1) and is addressed in section 4.4 of the PALFORZIA SmPC.
Subject is in "build-up phase" of immunotherapy to another allergen (ie, has not reached maintenance dosing)	Including patients starting with immunotherapy (build-up phase) to another allergen could confound the safety evaluation of PALFORZIA.	No	There are no additional safety concerns once patients are on maintenance allergen immunotherapy. The PALFORZIA SmPC (section 4.4) advises that PALFORZIA has not been studied in subjects receiving concomitant allergen immunotherapy and that caution should be exercised when administering PALFORZIA in conjunction with other allergen immunotherapies as the potential for severe

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
			allergic reactions may be enhanced.
Severe asthma (2007 NHLBI Criteria Steps 5 or 6) Mild or moderate asthma (2007 NHLBI Criteria Steps 1-4), if uncontrolled or difficult to control as defined by any of the following: FEV1 < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 5% of predicted, with or without controller medications (only for age 6 or greater and able to do spirometry) or Inhaled corticosteroids (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICS based on NHLBI dosing chart) or One hospitalisation in the past year for asthma or Emergency room (ER) visit for asthma within six months prior to screening	Uncontrolled asthma is a risk factor for fatal anaphylaxis (Brough, 2015) and patients with severe asthma are known to have an increased risk of allergic reactions including acute bronchospasm (Summers, 2008).	No	It is well-known that anaphylactic reactions may induce bronchospasm and wheezing. Patients requiring maximal therapy for asthma can poorly tolerate any additional respiratory component of an anaphylactic reaction. The same is true for mild or moderate asthmatics who are poorly controlled who may be at increased risk for respiratory compromise during an allergic reaction. However the risk of life-threatening bronchospasm is greater in patients with severe asthma (relative risk, 6.8 [4.1-11.3]) compared with patients with milder asthma (2.7 [1.7-4.0]) (Summers, 2008). Use in patients with current severe or uncontrolled asthma is addressed in the contraindications and warnings and precautions sections (section 4.3 and section 4.4 respectively) of the PALFORZIA SmPC.
History of corticosteroid medication use (via intravenous [IV], intramuscular [IM] or oral administration) in any of the following manners: History of daily oral steroid dosing for > 1 month during the past year Short term oral (IM or IV) steroid course in the	These patients were excluded as corticosteroids decrease inflammation and suppress the immune system which could have confounded the efficacy and safety evaluation of PALFORZIA in the clinical trials.	No	There are no known or expected adverse outcomes due to the co-administration of PALFORZIA and corticosteroids. The PALFORZIA SmPC advises that PALFORZIA has not been studied in patients on long-term systemic corticosteroid therapy.

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
past 3 months prior to randomisation > 2 short-term oral (IM or IV) steroid courses in the past year of at least 1 week duration			
Current or past use of other forms of peanut (or any food for ARC101) immunotherapy (eg, oral, sublingual, epicutaneous)	Concomitant or past peanut immunotherapy could have affected the efficacy and safety evaluation of PALFORZIA in clinical trials.	No	In clinical practice it is possible that patients will have been previously treated with other forms of peanut or other food immunotherapy. However, this should not prevent the use of PALFORZIA in these patients. The PALFORZIA SmPC advises that PALFORZIA has not been studied in patients receiving concomitant allergen immunotherapy and that caution should be exercised when administering PALFORZIA in conjunction with other allergen immunotherapies as the potential for severe allergic reactions may be enhanced.
History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria) and hereditary or idiopathic angioedema	Patients with mastocytosis have a high risk of developing severe anaphylaxis (Valent, 2014). These patients were excluded as their inclusion could have affected the safety evaluation of PALFORZIA in the study and put these patients at increased risk of anaphylaxis or anaphylactic shock.	No	Patients with a history of a severe mast cell disorder are unlikely to be treated with PALFORZIA in clinical practice as use in patients with a history of, or current, severe mast cell disorder is contraindicated in section 4.3 of the PALFORZIA SmPC.
Allergy to oat	This population was excluded from Study ARC003 and ARC010 as oat flour was used for the placebo oral food challenge in these studies. Including these patients would have put them at increased risk	No	PALFORZIA does not include oat-based excipients.

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
	of an allergic reaction and confounded the safety and efficacy results.		
Hypersensitivity to epinephrine and any of the excipients in the product	Similar to the majority of clinical trials, patients with hypersensitivity to any of the excipients were excluded from participation as their inclusion would have affected the efficacy and safety evaluation of PALFORZIA in the clinical trials. Patients with hypersensitivity to epinephrine were also excluded as epinephrine is key to treating anaphylaxis associated with PALFORZIA and their inclusion could have put these patients at increased risk of a fatal outcome.	No	All patients treated with PALFORZIA must be prescribed self-injectable epinephrine and instructed (or their parents/caregivers instructed) on the proper use of emergency self-injection of epinephrine in the case of an allergic reaction. In clinical practice patients with hypersensitivity to any of the excipients of PALFORZIA are not expected to be treated with PALFORZIA as it is contraindicated in this population (section 4.3 of the PALFORZIA SmPC). The PALFORZIA SmPC provides comprehensive guidance on the importance of using epinephrine in the case of anaphylaxis through instructing patients and/or caregivers to recognise the signs and symptoms of an allergic reaction and in the proper use of epinephrine according to the SmPC and package leaflet (PL). Immediate medical care should be sought upon its use and PALFORZIA treatment stopped until the patient has been evaluated by a physician.
Having the same place of residence as another subject in the study or any peanut OIT study	This population was excluded as the participants may have been randomised to differing treatment arms. In this case, the treatments might be mixed up, putting the participants at risk	No	As peanut allergy is strongly heritable, with concordance rates of 64% for monozygotic twins compared with 7% for dizygotic twins (Sicherer, 2000) and other siblings (Hourihane, 1996;

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
	and confounding the study results.		Stiefel, 2017), it is likely that some patients will be treated concurrently within the same family in clinical practice. The potential for medication errors is discussed in Section SVII.1.1.

Exclusion criteria for patients aged 1 to 3 years in study ARC005 that are specific to this population are discussed below. Other exclusion criteria that are applicable to this study are discussed above.

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
History of food protein-induced enterocolitis syndrome (FPIES) within 12 months before screening.	FPIES is a type of non-IgE mediated food allergy that can present with severe vomiting, diarrhoea and dehydration. Like other food allergies, FPIES reactions are triggered by eating a particular food and the most common triggers include cow milk, soy and grains (rice, barley, oats). The most severe forms of FPIES can lead to drop in energy, change in body temperature and low blood pressure leading to hospitalisation. Including these patients could have affected the safety evaluation of PALFORZIA in the clinical trial.	No	In clinical practice patients with a history of FPIES in the past 12 months (applicable for patients aged 1-3 years) are not expected to be treated with PALFORZIA as it is contraindicated in this population (section 4.3 of the PALFORZIA SmPC). Healthcare professionals are also advised that for chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups, or food refusal and failure to thrive especially assessed in toddlers and younger patients (ages 1 to 3 years), the potential for a diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE should be considered (section 4.4 of the PALFORZIA SmPC). Additionally, FPIES, a

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
			food-associated non-IgE mediated gastrointestinal disease that may occur in toddlers, should be considered in any toddler with significant food associated GI symptoms.
History of failure to thrive or any other form of abnormal growth, or developmental or speech delay that precludes age-appropriate communication.	This population was excluded from study ARC005 as including these patients could have affected the safety evaluation of PALFORZIA in the clinical trial.	No	In clinical practice patients with a history of failure to thrive (applicable for patients aged 1-3 years) are not expected to be treated with PALFORZIA as it is contraindicated in this population (section 4.3 of the PALFORZIA SmPC). Healthcare professionals are also advised that for chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups, or food refusal and failure to thrive especially assessed in toddlers and younger patients (ages 1 to 3 years), the potential for a diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE should be considered (section 4.4 of the PALFORZIA SmPC).
Allergy to oat or rice	Allergy to oat was an exclusion criterion in studies ARC003 and ARC010 as historically oat flour was used for the placebo oral food challenge in these studies. In ARC005 the placebo consisted of all excipients filled in matching capsules or sachets as PALFORZIA. Including patients with an allergy to oat or rice in ARC005 may have affected the efficacy and safety results if delays to	No	Often patients with allergies may have multiple allergies. There are no known or expected adverse outcomes for PALFORZIA treatment in patients with allergies to oat or rice in clinical practice as PALFORZIA does not contain oat or rice.

Criteria	Reason for exclusion	Considered missing information? (Yes/No)	Rationale if not considered missing information
	treatment or use of epinephrine were required in these patients related to these allergies.		

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Available data from the clinical development programme is unlikely to detect certain types of adverse reactions such as adverse reactions with an incidence of < 1/1000, or those caused by prolonged exposure beyond 2 years.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 13: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Use during pregnancy is an area of missing information (Section SVII.3.2).
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	• Patients with hepatic impairment were not included in the clinical development programme.
• Patients with renal impairment	• Patients with renal impairment were not included in the clinical development programme.
• Patients with cardiovascular impairment	• Patients with cardiac impairment were not included in the clinical development programme. Patients with a history of cardiovascular disease, including uncontrolled or inadequately controlled hypertension were excluded from clinical trial participation (Section SIV.1).
• Immunocompromised patients	• Immunocompromised patients were not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	• The target population is representative of the population evaluated in the clinical development programme.
Population with relevant different ethnic origin	In studies ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, ARC010, and ARC011 (combined), the majority of patients aged 4 years and older treated with PALFORZIA were White (947 of 1242 subjects) compared with Not white (295 of 1242 subjects) (Table 5 in Module SIII). Subjects with missing or inconsistent race values are excluded from the analysis. No meaningful differences in the incidence of adverse events by race (white, non-white) were observed in the PALFORZIA and placebo groups in the controlled or integrated safety populations (Module 2.7.4, Section 5.1.1). In ARC005, the majority of patients aged 1 to 3 years treated with PALFORZIA were White (67.3%), followed by Asian (18.4%), Other (8.2%), Black or African American (4.1%), and Not collected (4.1%) (Table 10 in Module SIII). Ethnicity data were also collected in this study. The majority of patients treated

Type of special population	Exposure
	with PALFORZIA were Not Hispanic or Latino (76.5%) compared with 5.1% Hispanic or Latino; 18.4% Not collected (Table 11 in Module SIII).
Subpopulations carrying relevant genetic polymorphisms	Not assessed in the clinical development programme. Patients were included based on clinical criteria and laboratory criteria.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

As of 30 January 2024, PALFORZIA is marketed for use in the US, EU (Germany, Austria, Sweden, and France), Switzerland and the UK.

SV.1.1 Method used to calculate exposure

For Germany, Austria, Switzerland and the UK, patient exposure is based on the shipment data for Initial Dose Escalation (IDE), up-dose and maintenance level shipment orders, which are provided upon orders received from a healthcare setting (hospital, physician or pharmacy) in these countries (Table 14). The release of IDE kits to a distributor or a healthcare setting does not unequivocally equate to a specific patient exposure. Therefore, the estimates provided for these countries represent potential patient exposures, as the IDE kits can be used for one patient only.

In the US PALFORZIA is only available to patients through the PALFORZIA Risk Evaluation and Mitigation Strategy (REMS) Program. PALFORZIA REMS is a safety program required by the Food and Drug Administration (FDA) to manage the risk of anaphylaxis associated with PALFORZIA and to ensure the potential benefits of PALFORZIA outweigh its risks. As patients who are prescribed PALFORZIA in the US must be enrolled in the PALFORZIA REMS Program, the exact number of US patients is known and some demographic data are available for these patients (Table 15).

Based on a request from the Pharmacovigilance Risk Assessment Committee (PRAC), an estimation for EU/EEA shipment data for up-dose and maintenance level packaging of PALFORZIA is available although the shipment information over the 12-month PSUR period (31 Jan 2023 to 30 Jan 2024) corresponds to an unknown number of patients, particularly during the up-dosing period (Table 16). Each dose level of PALFORZIA during the up-dosing period contains approximately a two-week supply (16 capsules) of product. Multiple shipments to a pharmacy for a single patient will have occurred during the period.

SV.1.2 Exposure

Table 14: Post-authorisation exposure to PALFORZIA by region outside the US from first authorisation (31 January 2020) to 30 January 2024

Region	Patients exposed (31 January 2020 to 30 January 2024)
EU (Germany and Austria)[1]	823
Switzerland[1]	36
UK[1]	326
Total:	1185

Source: PSUR No. 6 (31-Jan-2023 to 30-Jan-2024) Table 5.

EU = European Union; IDE = Initial Dose Escalation; PSUR = periodic safety update report; UK = United Kingdom.

[1]Estimated exposure based on IDE shipment orders

Table 15: Patient exposure to PALFORZIA during the REMS program from first authorisation (31 January 2020) to 30 January 2024

	Patients exposed (31 January 2020 to 30 January 2024)
Patients	
Total[1]	3591
Sex, n (%)	
Male	2178 (60.7)
Female	1411 (39.3)
Other	1 (<0.1)
Male, Other	1 (<0.1)
Age at Shipment[2] n (%)	
0 through 3 years	3 (0.1)
4 through 12 years	2378 (66.2)
13 through 17 years	1196 (33.3)
18 years or older	14 (0.4)

Source: PSUR No. 6 (31-Jan-2023 to 30-Jan-2024) Table 4.

PSUR = periodic safety update report; REMS = Risk Evaluation and Mitigation Strategy; US = United States.

[1]Patients who have received at least 1 dispense of PALFORZIA during the reporting period indicated, regardless of the reporting period in which they were enrolled. Used as the denominator for percentages.

[2]Patient age at first shipment.

Table 16: PALFORZIA shipments for up-dose* and maintenance levels from 31 Jan 2023 to 30 Jan 2024

Number of patients exposed	**All Up-dosing Level Shipments**	**All Maintenance Level Shipments**
EU (Germany and Austria)	4107	1801
Switzerland	688	59
UK	2029	447

*Shipments of 15 count 300 mg sachets are included with up-dose data; shipments of 30 count 300 mg sachets are included as maintenance level shipments.

Source: PSUR No. 6 (31-Jan-2023 to 30-Jan-2024) Table 6.

Abbreviations: EU = European Union; UK = United Kingdom.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Specific clinical studies evaluating abuse potential have not been conducted but there is no clinical evidence suggesting that PALFORZIA has any potential for drug abuse or misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table 17: Safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risks	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis
Important potential risks	Possible rebound after discontinuation of treatment
Missing information	Use during pregnancy Impact on long-term immune-mediated reactions

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no changes to the safety concerns.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
Potential Mechanisms	Most episodes of anaphylaxis to food are triggered through an immunologic mechanism involving IgE which leads to mast cell and basophil activation and the subsequent release of inflammatory mediators such as histamine, platelet activating factor, leukotrienes, tryptase and prostaglandins (Fischer, 2018). Because PALFORZIA is the antigen to which these patients are allergic, the underlying mechanism of allergic reactions to PALFORZIA is exactly the same. Similar to any form of desensitisation immunotherapy for treatment of allergic disease, the administration of escalating amounts of allergen to allergic individuals, starting with minute quantities of the allergen and steadily increasing the exposure over time, results in the degranulation of mast cells and basophils bearing antigen specific IgE bound to FcεR1, which in turn can result in allergy symptoms. The controlled release of mediators of inflammation by mast cells and basophils renders these cells temporarily refractory to subsequent antigen mediated activation and granule release. Interruption of the desensitisation process allows these cells to reform their granules and to release granules following exposure to the relevant antigen. Missed doses of PALFORZIA may pose a significant risk to patients due to potential loss of desensitisation. The importance of continuous daily dosing is emphasised in the PALFORZIA SmPC with a specific section on managing consecutive missed doses. The second process that occurs simultaneously during desensitisation immunotherapy is modulation of the immune response. Antigenic stimulation results in an initial activation of an effector response as evidenced by the observed increase in antigen-specific IgE and IgG4. In study ARC003 a > 2-fold increase in peanut specific IgE was observed during the up-dosing period in the PALFORZIA treatment group. The elevated levels of IgG4 may competitively inhibit the binding of antigen to specific IgE molecules or binding to FcγR2b receptors, resulting in the induction of immunoreceptor tyrosine based inhibitory motif (ITIM) mediated inhibitory signalling. With repeated antigenic stimulation over a period of months, a regulatory immune response is also induced, as demonstrated by a decrease in antigen specific IgE levels and the emergence of a CD4+, CD25+, Foxp3+ population of T lymphocytes over time. The practical implication of these processes is that a patient undergoing allergen immunotherapy is unlikely to be fully protected from IgE mediated allergic adverse events for several months/years due to the time needed for immunomodulatory effects to occur. The incidence of treatment-related allergy adverse events generally decreased over time for over 52 weeks of treatment at 300 mg/day in the integrated safety population, but there were subjects who had allergic reactions with PALFORZIA during the maintenance

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	period (Module 2.7.4, Section 2.1.8.1). Although the majority of the reactions were mild to moderate, some were severe (Module 2.7.4, Table 39).
Evidence source and strength of evidence	Patients with peanut allergy may have allergic symptoms, including systemic allergic reactions, when treated with PALFORZIA as it contains defatted powder of *Arachis hypogaea L.*, semen (peanuts). *Systemic allergic reaction* is used to describe an anaphylactic reaction of any severity and *anaphylaxis* is used to describe an anaphylactic reaction that is severe. In the integrated safety population that evaluated PALFORZIA treatment in subjects aged 4 to 17 years, systemic allergic reactions of any severity were reported in 15.8% of subjects, including 0.6% during initial dose escalation, 8.7% during up-dosing and 10.5% during maintenance. Severe systemic allergic reaction (anaphylaxis) was reported in 1.1% subjects, including 0.4% subjects during up-dosing and 0.8% during maintenance at 300 mg/day. In study ARC005 that evaluated PALFORZIA treatment in subjects aged 1 to 3 years, systemic allergic reactions of any severity were reported in 8.2% of subjects treated with PALFORZIA, including 2.0% during up-dosing and 6.9% during maintenance. Systemic allergic reactions of any severity occurred in 8.3% of placebo treated subjects including 4.2% during up-dosing and 4.4% during maintenance. No severe or serious systemic allergic reactions occurred in either group. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Characterisation of the risk	<u>Controlled population</u> In the controlled population (841 subjects treated with PALFORZIA and 335 subjects treated with placebo in ARC003, ARC007, and ARC010), systemic allergic reactions by any trigger (study product, food allergen, other allergen) were reported in 9.2% of subjects in the PALFORZIA group and 3.3% of subjects in the placebo group during initial dose escalation and up-dosing combined (Module 2.7.4, Section 2.1.8.1). During 300 mg/day dosing, systemic allergic reactions were reported were reported in 7.4% PALFORZIA, 2.4% placebo in ARC010 and 8.7% PALFORZIA, 1.7% placebo in ARC003. Most systemic allergic reactions (>80%) in the PALFORZIA group were considered triggered by study product. Most subjects in the PALFORZIA group and all subjects in the placebo group had only one event of systemic allergic reaction: 7.3% PALFORZIA, 3.3% placebo during initial dose escalation and up dosing combined; 5.6% PALFORZIA, 0% placebo during 300 mg/day dosing in ARC010, and 7.4% PALFORZIA, 1.7% placebo during 300 mg/day dosing in ARC003. The majority of systemic allergic reactions were of mild or moderate severity: 8.7% of subjects in the PALFORZIA group and 3.3% of subjects in the placebo group during initial dose escalation and up-dosing combined; 7.4% PALFORZIA, 2.4% placebo during 300 mg dosing in ARC010, and 8.4% PALFORZIA, 1.7% placebo during 300 mg dosing in ARC003 (Module 2.7.4, Section 2.1.8.1). No subjects in ARC010 experienced anaphylaxis. In ARC003 4 subjects (0.5%) reported severe systemic allergic reaction (anaphylaxis) in the PALFORZIA group during initial dose escalation

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	and up-dosing combined and no placebo-treated subjects reported anaphylaxis during the same period. In the same study ARC003, 1 subject (0.3%) in the PALFORZIA group reported anaphylaxis compared with no placebo-treated subjects during 300 mg/day dosing. None of the severe systemic allergic reactions had a fatal outcome. Most subjects with a systemic allergic reaction continued study treatment. During initial dose escalation and up-dosing combined, 12 subjects (1.4%) in the PALFORZIA group discontinued due to a systemic allergic reaction, including 1 subject with anaphylaxis during up-dosing. During 300 mg/day dosing, no subject in ARC010 and 2 subjects (0.6%, including 1 with anaphylaxis) discontinued due to a systemic allergic reaction in ARC003. No subject in the placebo group discontinued due to a systemic allergic reaction. Most systemic allergic reactions were nonserious. No subject in ARC010 had a serious systemic allergic reaction. Three subjects in ARC003 (PALFORZIA group) had a serious systemic allergic reaction, including 2 during up-dosing (0.2%; 1 mild, 1 moderate) and 1 during 300 mg/day dosing (0.3%, anaphylaxis). Epinephrine was used for systemic allergic reactions in 5.7% of subjects in the PALFORZIA group and 2.7% of subjects in the placebo group during initial dose escalation and up-dosing combined; 3.7% PALFORZIA and 0% placebo during 300 mg/day dosing in ARC010, and 6.1% PALFORZIA and 1.7% placebo during 300 mg/day dosing in ARC003. Most epinephrine was not administered at the study site. The most common symptom (> 5% in any group) associated with a systemic allergic reaction in the controlled population was urticaria, followed by dyspnoea (Module 2.7.4, Section 2.1.8.1). <u>Integrated safety population</u> The overall summary of systemic allergic reactions for the integrated safety population is consistent with the results for the controlled population. In the integrated safety population, systemic allergic reactions by any trigger (study product, food allergen, other allergen) and severity were reported in 15.8% of subjects overall, including 0.6% during initial dose escalation, 8.7% during up-dosing, and 10.5% during all 300 mg/day dosing (Module 2.7.4, Section 2.1.8.1). During 300 mg/day dosing, the proportion of subjects with systemic allergic reactions by interval was 4.8% at 0–13 weeks, 4.3% at 14-26 weeks, 4.4% at 27–52 weeks, and 3.5% at > 52 weeks. Existing data suggest an increased risk of systemic allergic reaction for adolescents (21.9%) than for children (≤ 11 years; 11.9%). Most systemic allergic reactions (> 80%) were considered triggered by study product (Module 2.7.4, Section 2.1.8.1). After adjusting for exposure, event rates for systemic allergic reaction decreased from 1.18 events per subject-year during initial dose escalation to 0.25 during up-dosing and 0.24 through the first 12 weeks of maintenance. Exposure-adjusted event rates remained stable through > 52 weeks (0.21 events per subject year at 14-26 weeks, 0.21 at 27-52 weeks, and 0.20 at > 52 weeks) and were 0.24 overall (any dose of PALFORZIA).

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	Overall, 15.8% of subjects had a systemic allergic reaction and of these, most (69.7%) had only 1 event. Six subjects (0.6%) had a systemic allergic reaction during initial dose escalation and all had 1 event; 80 subjects (8.7%) during up-dosing (64, 1 event; 16, 2 events), and 81 subjects (10.5%) during 300 mg/day dosing (62, 1 event; 9, 2 events; 10, ≥ 3 events [reflecting the longer period of observation]). The majority of subjects had systemic allergic reactions of mild or moderate severity: 0.6% of subjects during initial dose escalation, 8.3% during up-dosing, and 9.7% during all 300 mg/day dosing. Severe systemic allergic reactions (anaphylaxis) was reported in 10 subjects (1.1% overall), including 4 subjects (0.4%) during up-dosing and 6 (0.8%) during all 300 mg/day dosing (0% at 0–13 weeks, 0.1% at 14–26 weeks, 1.1% at 27-52 weeks, and 0% at > 52 weeks); 1 of these events was considered serious. Discontinuation from studies due to systemic allergic reaction was low overall. Fifteen subjects (1.6%) treated with PALFORZIA discontinued due to systemic allergic reaction, including 3 subjects (0.3%) with anaphylaxis. Most systemic allergic reactions were non-serious. Four subjects had a serious systemic allergic reaction: 2 (0.2%) during up-dosing and 2 (0.3%) during all 300 mg/day dosing, including 1 anaphylaxis. Epinephrine was used for systemic allergic reactions in 10.8% of subjects overall (ie, about two-thirds [68.4%] of subjects with a systemic allergic reaction): 0.4% during initial dose escalation, 5.5% during up-dosing, and 7.5% during all 300 mg/day dosing. Most epinephrine was not administered at the study site. Epinephrine was used for anaphylaxis in 8 of 10 subjects (80%). The most common symptom associated with systemic allergic reactions was urticaria (0.4% initial dose escalation, 4.1% up-dosing, 7.3% all 300 mg/day dosing), followed by dyspnoea (0.1%, 3.7%, 5.3%), wheezing (0.2%, 3.2%, 4.4%), and cough (0.2%, 3.2%, 4.4%). All other symptoms were in less than 4% of subjects during any period (Module 2.7.4, Section 2.1.8.1). The incidence of treatment-related and hypersensitivity adverse events generally decreased over time for over 52 weeks of treatment at 300 mg/day in the integrated safety population (Module 2.7.4, Section 7). Follow-On Study ARC008[1] Overall in study ARC008, of the 596 subjects treated with PALFORZIA, 45 subjects (7.6%) had a total of 52 systemic allergic reactions (consistent with Medical Dictionary for Regulatory Activities [MedDRA] preferred term anaphylactic reaction) (Module 2.7.4, Section 2.1.9.4.6.1). The highest proportion of subjects with systemic allergic reaction (10.4%) was during initial maintenance for subjects who received placebo in the originating study (pathway 3), followed by initial dose escalation and up-dosing for subjects in pathway 3 (9.6%). The incidence of systemic allergic reaction in total extended maintenance was 6.2% and was similar for each time interval (3.5% for 0-3 months, 2.7% for 4-6 months, 3.6% for 7-9 months). No subject receiving PALFORZIA ≥ 10 months in extended maintenance had a systemic allergic reaction as of the data cutoff date (15 Dec 2018).

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	Overall, 38 subjects (6.4%) had 1 event and 7 subjects (1.2%) had 2 events of systemic allergic reaction. Three subjects had 2 events each during initial dose escalation and up-dosing in pathway 3, and 2 subjects had 2 events each during total extended maintenance. As this is an ongoing study, information is missing for 2 additional subjects who had 2 events due to the algorithm used to generate the data output. No subject had 3 or more events of systemic allergic reaction. All systemic allergic reactions were mild (3.9%) or moderate (3.7%) as assessed by the investigators using the 3-point EAACI grading scale. No subject had a systemic allergic reaction that was considered severe (anaphylaxis). The highest incidence of moderate systemic allergic reaction (8.3%) was during initial maintenance in pathway 3. One subject (pathway 1) had a systemic allergic reaction that was a serious adverse event and permanently discontinued study product due to the event. Overall, the study product was the most common trigger of systemic allergic reaction (40 events), followed by other food allergens (6 events), peanut or peanut containing food (4 events), and other (2 events). Study product was identified as the trigger for 19 events during total extended maintenance, 16 during initial dose escalation and up-dosing (pathway 3), 5 during initial maintenance (pathway 3), and 1 during up-dosing (pathway 2). Epinephrine use was required for about half (25 of 52) of events of systemic allergic reaction: 13 during total extended maintenance, 11 during initial dose escalation and up-dosing, and 1 each during maintenance for subjects in pathways 2 and 3. The most common individual symptom of systemic allergic reaction in all treatment periods combined was urticaria (4.5%), followed by wheezing (3.5%), cough (3.2%), pruritus (3.0%), and dyspnoea (2.3%). All other symptoms were reported in less than 2% of subjects. <u>Study ARC005</u> Overall in study ARC005, 8 PALFORZIA-treated subjects (8.2%) and 4 placebo-treated subjects (8.3%) had 1 or more systemic allergic reactions (Module 2.7.4, Section 2.1.13.8.1). All events occurred during up-dosing and maintenance; none occurred during initial dose escalation; 2 subjects (2.0%) PALFORZIA and 2 subjects (4.2%) placebo during up-dosing and 6 subjects (6.9%) PALFORZIA and 2 subjects (4.4%) placebo during maintenance. The 8 PALFORZIA-treated subjects experienced a total of 9 systemic allergic reactions (anaphylactic reactions) including 3 events triggered by PALFORZIA, none by peanut or peanut-containing food, and 6 by other food allergen. In the placebo group, 4 subjects experienced 4 events of systemic allergic reaction, all triggered by other food allergens. Overall, the maximum severity of systemic allergic reactions was mild for 2 subjects (2.0%) and moderate for 6 subjects (6.1%) in the PALFORZIA group. The maximum severity was mild and moderate for 2 subjects (4.2%) each in the placebo group. None of the systemic allergic reactions were severe or considered to be serious.

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	Epinephrine use was required for systemic allergic reactions in 5 subjects (5.1%) in the PALFORZIA group and 2 subjects (4.2%) in the placebo group. The symptoms associated with systemic allergic reactions in the PALFORZIA group were cough and urticaria (4 subjects each, 4.1%), throat irritation and wheezing (3 subjects each, 3.1%) and vomiting reported in 1 subject (1.0%). The subjects in the placebo group with systemic allergic reactions had associated symptoms of vomiting (3 subjects, 6.3%), cough (2 subjects, 4.2%), and urticaria and wheezing reported in 1 subject (2.1%) each. There were no study discontinuations due to a systemic allergic reaction in either treatment group. <u>Post-marketing data</u> Cumulatively during the post-marketing period from 31 January 2020 to 30 January 2024, a total of 116 cases (58 serious) of anaphylactic reaction were reported. This includes non-serious cases from spontaneous sources and that some cases might include more than one adverse reaction. In addition, five non serious cases were reported under the Lower Level Term (LLT) Systemic allergic reaction, cumulatively from the post-marketing experience.
Risk factors and risk groups	Patients are more likely to experience allergic symptoms in the presence of certain co-factors which are known to increase the likelihood of allergic reactions in general. These cofactors may be modifiable or non-modifiable. Modifiable co-factors may include exercise, hot bath or shower, alcohol consumption, fasting, or intake of non-steroidal anti-inflammatory medications. Non-modifiable co-factors may include intercurrent illness (eg, influenza or viral infection), an increase in severity of asthma, menstruation, stress, fatigue or sleep deprivation (Smith, 2015; Turner, 2017b; Varshney, 2009). In addition, patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment.
Preventability	Anaphylaxis/systemic allergic reactions can be managed in clinical practice and in a non-clinic setting through adhering to the guidance in the PALFORZIA SmPC. The PALFORZIA SmPC contraindicates use of PALFORZIA in patients who had severe or life-threatening anaphylaxis within 60 days before initiating treatment with PALFORZIA. The initial dose escalation, first dose of each new up-dosing level and first maintenance dose are to be administered under the supervision of a healthcare professional qualified in the diagnosis and treatment of allergic diseases and in a healthcare setting prepared to manage potential severe allergic reactions, including anaphylaxis. The careful observation during the initial dose escalation and first dose of each change of dose level during up-dosing allows healthcare professionals the opportunity to recognise allergic symptoms and to treat the patient before they progress to a systemic allergic reaction. The prolonged period of up-dosing is designed to lessen the chance of a systemic allergic reaction to PALFORZIA while allowing desensitisation to progress. Dose modification guidelines for those who experience allergic symptoms are clearly stated in the PALFORZIA SmPC.

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	Healthcare professionals are advised in the PALFORZIA SmPC that patients should avoid taking hot showers, baths or exercising immediately prior to or within 3 hours after consuming PALFORZIA, exercise should be avoided immediately prior to or following 3 hours of treatment and to delay taking a dose of PALFORZIA until after strenuous exercise signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, rapid heart rate) have subsided. Each dose of PALFORZIA should be consumed with a meal and alcohol (including medicinal products containing alcohol) should not be taken for 2 hours before or 2 hours after a dose. PALFORZIA should not be taken within 2 hours of bedtime. The potential for allergic reactions to occur if taking NSAIDs whilst on PALFORZIA treatment should also be considered. If the patient has an intercurrent illness or an exacerbation of asthma the patient and/or caregiver should be instructed to seek medical advice before taking their next dose of PALFORZIA. Furthermore, withholding or decreasing the PALFORZIA dose temporarily should be considered based on individual patient needs if the patient is experiencing menstruation, stress, fatigue or sleep deprivation. Patients and/or their caregivers should be educated to recognise the signs and symptoms of allergic reactions and instructed when to seek immediate medical care should any of these occur. All patients with significant food allergies, including those on PALFORZIA, should be prescribed self-injected epinephrine, and the patient and/or their caregiver should be instructed in its use. Healthcare professionals are advised that if treatment with PALFORZIA is stopped, patients must continue to carry self-injectable epinephrine at all times.
Impact on the risk-benefit balance of the product	Anaphylaxis is a severe, systemic allergic reaction that is potentially life-threatening if not promptly treated. While anaphylaxis can be associated with immunotherapy, including PALFORZIA, it is also the most important risk for patients with peanut allergies. As described above, allergen desensitisation involves acute desensitisation occurring over a period of weeks to months and immunomodulation occurring over a period of months to years. Therefore, the risk of anaphylaxis and systemic allergic reactions with PALFORZIA is expected to decrease over time. In the clinical development programme PALFORZIA has demonstrated efficacy desensitising patients with peanut allergy. The proportion of subjects who tolerated a single highest dose of at least 1000 mg peanut protein with no more than mild symptoms at the exit DBPCFC (primary efficacy endpoint) was 50.3% for the PALFORZIA group and 2.4% for the placebo group with a treatment difference of 47.8% (95% CI: 38.0, 57.7; $p < 0.0001$) in study ARC003 and similarly 58.3% for the PALFORZIA group and 2.3% for the placebo group with a treatment difference of 56.0% (95% CI: 44.1, 65.2; $p < 0.0001$) in study ARC010 (Module 2.7.3, Table 14). The key secondary efficacy endpoints were also met. The proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC (key secondary efficacy endpoint) was 67.2% for the PALFORZIA group and 4.0% for the placebo group with a treatment difference of 63.2% (95% CI: 53.0, 73.3; $p < 0.0001$) in study ARC003 and similarly 68.2% for the PALFORZIA group and

Important Identified Risk 1: Anaphylaxis/systemic allergic reactions	
	9.3% for the placebo group with a treatment difference of 58.9% (95% CI: 44.2, 69.3; p < 0.0001) in study ARC010. The proportion of subjects who tolerated a single highest dose of at least 300 mg peanut protein with no more than mild symptoms at the exit DBPCFC (key secondary efficacy endpoint) was 76.6% for the PALFORZIA group and 8.1% for the placebo group with a treatment difference of 68.5% (95% CI: 58.6, 78.5; p < 0.0001) in study ARC003 and similarly 73.5% for the PALFORZIA group and 16.3% for the placebo group with a treatment difference of 57.2% (95% CI: 41.2, 69.1; p < 0.0001) in study ARC010 (Module 2.7.3, Table 14). In study ARC005, the proportion of subjects aged 1 to 3 years who tolerated a single dose of 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC was 73.5% for the PALFORZIA group and 6.3% for the placebo group with a treatment difference of 67.2% (95% CI: 50.0, 84.5; p < 0.0001) (ARC005 CSR, section 13.1). In the same study, the proportion of subjects who tolerated a single dose of 1000 mg peanut protein was 68.4% for the PALFORZIA group and 4.2% for the placebo group with a treatment difference of 64.2% (95% CI: 47.0, 81.4; p < 0.0001). The benefit of PALFORZIA as an effective OIT for desensitising peanut allergic patients outweighs the risk of anaphylaxis/systemic allergic reactions which likely decreases over time and can be managed in clinical practice through patient selection and education, close patient monitoring, and use of epinephrine. Anaphylaxis/systemic allergic reactions will be further characterised in an open-label, longer-term follow-on study (ARC008[1]) that will evaluate safety data for patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation (Part III).
Public health impact	Peanut allergy affects 1% to 3% of children in many westernised countries (Fleischer, 2015; Turner, 2017a) and the estimated incidence of fatal peanut anaphylaxis is 0.73–4.25 per million person-years (Umasunthar, 2013). While fatalities due to peanut allergy are rare, anaphylaxis to peanut is more common. In a registry of 1070 children with peanut allergy, 35% reported an episode of anaphylaxis over a 5-year period of observation (Leickly, 2018). Most systemic allergic reaction events after PALFORZIA did not reach the level of severity associated with the term anaphylaxis. Anaphylaxis (severe) was reported in 1.1% PALFORZIA treated patients. Taking into account the risk of significant and fatal peanut anaphylaxis in the peanut allergic population and that the risk of anaphylaxis decreases once maintenance with PALFORZIA is achieved, the overall public health impact is positive.

[1] Study ARC008 is complete but as the CSR is currently under preparation it is still considered an ongoing study.

Important Identified Risk 2: Eosinophilic oesophagitis	
Potential Mechanisms	Eosinophilic oesophagitis (EoE) is a chronic, local immune-mediated oesophageal clinicopathologic disease, characterised clinically by symptoms related to oesophageal dysfunction and pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation (Lucendo, 2017;

Important Identified Risk 2: Eosinophilic oesophagitis	
	Liacouras, 2011). One or more biopsy specimens must show eosinophilic inflammation usually defined as ≥ 15 eosinophils per high power field for a diagnosis to be confirmed (Liacouras, 2011). Unlike other segments of the gastrointestinal tract, the oesophagus is normally devoid of eosinophils (Mishra, 2002). Eosinophilic oesophagitis results from a complex interplay between genetic, environmental, and host immune system factors. The involvement of allergic mechanisms in the pathogenesis of EoE is supported by studies showing oesophageal tissue expression of mediators such as immunoglobulin E (IgE), eotaxin-3, interleukin-13 (IL-13), and interleukin-5 (IL-5), and cell mediators including mast cells, dendritic cells, as well as eosinophils (Rothenberg, 2009). Type 2 helper T (Th2) cell cytokines also play an important role in disease pathogenesis (Rothenberg, 2009). While the prevalence of EoE is estimated to be about 1 in 2500 in the general population, a study reported a prevalence of 4.72% among patients with food allergy (Hill, 2017). In a longitudinal birth cohort study, Hill et al found that there was a correlation with primary allergic diagnoses such as atopic dermatitis and asthma with EoE, but that the correlation was especially strong when there was a primary diagnosis of IgE-mediated food allergy (Hill, 2018). Thus, there is a significant background occurrence of EoE in patients with food allergy. In addition, EoE has been reported in patients undergoing OIT for treatment of food allergy. Lucendo et al undertook a systematic review of the association between OIT and EoE (Lucendo, 2014). This review revealed that up to 2.7% of patients with IgE-mediated food allergy undergoing OIT may develop EoE. However, the authors noted a significant publication bias indicating that the association may be less robust. Other published literature suggests a 2.5% to 7.3% incidence of biopsy confirmed EoE emerging during treatment of food allergy with OIT (Hill, 2017). However, it has been shown that some adult patients have significant oesophageal eosinophilia prior to starting OIT. In one study 48% of subjects treated with peanut oral immunotherapy had gastrointestinal eosinophilia at baseline based on serial esophagogastroduodenoscopies (EGD) (Wright, 2018), even in the absence of symptoms consistent with EoE. This study highlights the difficulty in determining the contribution of OIT to the development of EoE when the patient's underlying allergy is also strongly associated with EoE.
Evidence source and strength of evidence	Eosinophilic oesophagitis is a significant allergic condition which if left untreated can cause lasting damage to the oesophagus. EoE has been reported for other OIT used to treat food allergies. In the integrated safety population, EoE was diagnosed in 5 of 944 subjects (0.5%) with a further 7 cases in other studies (1 subject in ARC001, 1 subject in ARC002, 1 adult subject in ARC004, and 4 subjects in ARC008[1]) to total 12 of 1217 subjects (approximately 1%) treated with PALFORZIA experiencing EoE. After PALFORZIA was discontinued symptoms were considered recovered/resolved or recovering/resolving in all 12 subjects.

Important Identified Risk 2: Eosinophilic oesophagitis	
	In study ARC005, EoE was not diagnosed in any subject in either treatment group. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed for other OIT and the predicted mechanism.
Characterisation of the risk	Eosinophilic oesophagitis is a disease with the unique features of chronic oesophagitis, atopy, immune sensitisation to oral antigens, reversibility and familial association (Rothenberg, 2009). EoE has a variety of nonspecific symptoms, such as feeding difficulty, nausea and vomiting, heartburn, and failure to thrive in children, while in adults, dysphagia, pain on swallowing (odynophagia) and food impaction may occur. Prolonged inflammation evokes structural alterations and an increased risk of food impaction (Straumann, 2008). The disease can lead to a considerably reduced Quality of Life (QoL) (Lucendo, 2017). No subjects participating in PALFORZIA clinical trials underwent endoscopies prior to enrolment, so no baseline assessments of tissue eosinophilia were available prior to treatment with PALFORZIA. <u>Controlled population</u> As noted previously, in the controlled population of subjects participating in PALFORZIA clinical trials, EoE was diagnosed in 3 of 841 PALFORZIA treated subjects (0.4%) during up-dosing and in no subjects during dosing with 300 mg/day in ARC003 or ARC010 (Module 2.7.4, Section 2.1.8.5). <u>Integrated safety population</u> In the integrated safety population of 944 subjects, EoE was diagnosed in 2 additional PALFORZIA-treated subjects (1 during up-dosing and 1 during 300 mg/day dosing). EoE was considered treatment related in 3 of the subjects (0.3% overall). The severity of EoE was considered mild in 2 subjects (0.2%), moderate in 2 subjects (0.2%), and severe in 1 subject (0.1%). All 5 subjects with EoE discontinued from the study, including 1 who was discontinued due to no longer meeting eligibility criteria. <u>Other studies</u> Outside of the integrated safety population, 7 additional subjects had a diagnosis of EoE in other studies including 2 subjects in the phase 2 studies ARC001 (1 subject) and ARC002 (1 subject), 1 adult subject in study ARC004, and 4 subjects in study ARC008[1]. Clinical review of all the cases of EoE indicated that the onset of clinical symptoms was typically with dysphagia, vomiting, or both. The diagnosis of EoE was confirmed by esophagogastroduodenoscopy in all but one case, which was diagnosed based on clinical features. Most subjects were discontinued from PALFORZIA treatment and treated with a proton pump inhibitor with or without a topical corticosteroid. After PALFORZIA was discontinued symptoms were considered recovered/resolved or recovering/resolving in all 12 subjects. <u>Study ARC005</u>

Important Identified Risk 2: Eosinophilic oesophagitis	
	EoE was not diagnosed in any subject in study ARC005. Post-marketing data Cumulatively during the post-marketing period from 31 January 2020 to 30 January 2024, a total of 24 cases (7 serious) of EoE were reported.
Risk factors and risk groups	A strong association between IgE-mediated food allergy and EoE has been observed (Greenhawt, 2014; Spergel, 2012). Consequently, patients with IgE-mediated food allergy who encounter the food to which they are allergic, either naturally or during OIT, are at increased risk of EoE. It remains unclear whether OIT induces EoE or causes pre-existing EoE to become symptomatic (Wright, 2018). The aetiology of EoE is multifactorial and unlike food anaphylaxis, which occurs in an estimated 15% of EoE patients (Assa'ad, 2007), patients with EoE are polysensitised to a variety of foods suggesting a general breakdown in oral antigen tolerance (Rothenberg, 2009). Male sex is a strong risk factor for EoE both in children and adults (Arias, 2016). Eosinophilic oesophagitis may occur at any age but there is a rising incidence in children with age and a peak in adults at 30–50 years with most cases occurring in children, adolescents, and adults younger than 50 years (Lucendo, 2017). A retrospective database analysis over a period of 8 years found that in 89 paediatric patients with EoE up to 18 years of age, male sex (78.6%), white race (94.4%), young age at diagnosis (mean ± SD, 6.2 ± 4.8 years), and atopy with sensitisation to environmental and food allergens in 79% and 75%, respectively, were prevalent (Assa'ad, 2007). The associated conditions extracted from the past medical history of the 89 patients or reported by the parents were atopy (asthma, allergic rhinitis, eczema, anaphylaxis to food, and allergic conjunctivitis in 39%, 30%, 19%, 9%, and 8%, respectively); immunologic (recurrent infections and autoimmune disorders in 13% and 2%, respectively); and developmental and neurologic (developmental delay, seizures, cerebral palsy, autism in 12%, 6%, 4%, and 1%); and chromosomal abnormalities in 1% patients (Assa'ad, 2007). EoE patients usually suffer from a high number of concomitant atopic disorders including rhinitis, asthma and eczema. A recent systematic review of 21 studies comprising 53,542 EoE patients and 54,759 controls found that allergic rhinitis was significantly more common among patients with EoE compared with control subjects as were bronchial asthma and eczema. (González-Cervera, 2017). Eosinophilic oesophagitis has a strong familial association (Rothenberg, 2009). Nearly 10% of parents of EoE patients have a history of oesophageal strictures and an estimated 8% have biopsy proven EoE (Noel, 2004). In a study out of the 103 paediatric patients 73.5% had a family history of atopic disease, 6.8% a family history of EoE, 9.7% a family history of oesophageal dilatation, 57.4% rhinoconjunctivitis, 36.8% wheezing and 46% possible food allergy (Noel, 2004).
Preventability	Patients with peanut allergies are at risk for EoE due to their underlying food allergy. Healthcare professionals are advised that use of PALFORZIA is

Important Identified Risk 2: Eosinophilic oesophagitis	
	contraindicated in patients with a history of, or current EoE, other eosinophilic gastrointestinal disease, chronic, recurrent, or severe GERD, or dysphagia. The guidance in the PALFORZIA SmPC highlights that EoE has been reported with PALFORZIA. Dose modifications may be considered in patients who develop chronic or recurrent gastrointestinal symptoms. For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups, or food refusal and failure to thrive especially assessed in toddlers and younger patients (ages 1 to 3 years), the potential for a diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE should be considered. PALFORZIA must be discontinued in patients who experience severe or persistent gastrointestinal symptoms including dysphagia, gastroesophageal reflux, chest pain or abdominal pain and a diagnosis of EoE should be considered. The guidance to withdraw PALFORZIA treatment is based on clinical trial experience during which the majority of patients had improvement of symptoms following cessation of therapy. It is also in line with other studies which have shown that EoE induced by OIT resolves in most cases after discontinuation of OIT (Lucendo, 2014).
Impact on the risk-benefit balance of the product	The presenting symptoms of EoE show a different pattern of clinical presentation between young children and adults (Lucendo, 2017). Untreated EoE is usually associated with persistent symptoms and inflammation, which can lead to oesophageal remodelling, stricture formation, and functional abnormalities. However, EoE is not normally life-threatening. Symptoms are often reversible when the allergen is removed from the diet or OIT is discontinued. The EoE cases observed in the PALFORZIA clinical trials were non-serious and the majority were of mild or moderate severity (Module 2.7.4, Section 2.1.8.5). None of the EoE cases were life-threatening or fatal. This is similar to other OIT studies in which symptoms resolved promptly upon cessation of OIT (Hill, 2017). As mentioned, rates of EoE with OIT reported in the literature range from 2.5% to 7.3%. There were 12 reports of EoE in the entire PALFORZIA program of 1217 exposed patients for a rate of 1%. In the clinical development programme PALFORZIA has demonstrated efficacy desensitising patients with peanut allergy. The proportion of subjects who tolerated a single highest dose of at least 1000 mg peanut protein with no more than mild symptoms at the exit DBPCFC (primary efficacy endpoint) was 50.3% for the PALFORZIA group and 2.4% for the placebo group with a treatment difference of 47.8% (95% CI: 38.0, 57.7; $p < 0.0001$) in study ARC003 and similarly 58.3% for the PALFORZIA group and 2.3% for the placebo group with a treatment difference of 56.0% (95% CI: 44.1, 65.2; $p < 0.0001$) in study ARC010 (Module 2.7.3, Table 14). The key secondary efficacy endpoints were also met. The proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC (key secondary efficacy endpoint) was 67.2% for the PALFORZIA group and 4.0% for the placebo group with a treatment

Important Identified Risk 2: Eosinophilic oesophagitis	
	difference of 63.2% (95% CI: 53.0, 73.3; p < 0.0001) in study ARC003 and similarly 68.2% for the PALFORZIA group and 9.3% for the placebo group with a treatment difference of 58.9% (95% CI: 44.2, 69.3; p < 0.0001) in study ARC010. The proportion of subjects who tolerated a single highest dose of at least 300 mg peanut protein with no more than mild symptoms at the exit DBPCFC (key secondary efficacy endpoint) was 76.6% for the PALFORZIA group and 8.1% for the placebo group with a treatment difference of 68.5% (95% CI: 58.6, 78.5; p < 0.0001) in study ARC003 and similarly 73.5% for the PALFORZIA group and 16.3% for the placebo group with a treatment difference of 57.2% (95% CI: 41.2, 69.1; p < 0.0001) in study ARC010 (Module 2.7.3, Table 14). In study ARC005, the proportion of subjects aged 1 to 3 years who tolerated a single dose of 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC was 73.5% for the PALFORZIA group and 6.3% for the placebo group with a treatment difference of 67.2% (95% CI: 50.0, 84.5; p < 0.0001) (ARC005 CSR, section 13.1). In the same study, the proportion of subjects who tolerated a single dose of 1000 mg peanut protein was 68.4% for the PALFORZIA group and 4.2% for the placebo group with a treatment difference of 64.2% (95% CI: 47.0, 81.4; p < 0.0001). Overall, the benefit of PALFORZIA as an effective OIT for desensitising peanut allergic patients and therefore decreasing the risk of life-threatening anaphylaxis outweighs the risk of EoE which can be managed in clinical practice through patient selection, monitoring and treatment withdrawal. Eosinophilic oesophagitis will be further characterised in an open-label, longer-term follow-on study (ARC008[1]) that will evaluate safety data for patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation (Part III).
Public health impact	In the controlled population, EoE was diagnosed in 3 of 841 PALFORZIA treated subjects (0.4%) during up-dosing and no subjects during dosing with 300 mg/day in ARC003 or ARC010. In the integrated safety population of 944 subjects, EoE was diagnosed in 2 additional subjects (1 during up-dosing and 1 during 300 mg/day dosing) for an overall incidence of 0.5%. In total there were 12 cases of EoE reported in 1217 patients receiving PALFORZIA for a rate of approximately 1%. This compares to the published literature, which suggests a 2.5% to 7.3% incidence of biopsy confirmed EoE emerging during treatment of food allergy with OIT (Hill, 2017). EoE was not diagnosed in any subject in study ARC005. Overall, the public health impact of EoE induced by PALFORZIA is expected to be low given the expected reduction in anaphylaxis in peanut allergic patients treated with PALFORZIA.

[1]Study ARC008 is complete but as the CSR is currently under preparation it is still considered an ongoing study.

Important Potential Risk 1: Possible rebound after discontinuation of treatment	
Potential Mechanisms	Immunologic assessments in PALFORZIA clinical studies show that serum ps-IgE increases (concentrations measured in ng/mL), reaches a peak, and

Important Potential Risk 1: Possible rebound after discontinuation of treatment	
	subsequently decreases to approach pre-treatment baseline levels over the first year of PALFORZIA treatment. In contrast, serum ps-IgG4 (concentrations measured in mg/mL) increases over the first year of treatment and continues to increase throughout the second year of treatment (data shown in CSR ARC004, Section 11.4.1.5). Published literature suggests OIT-induced elevations of ps-IgG4 competitively inhibit the binding of allergen to IgE (Kulis, 2018; Vickery, 2013; Jones, 2009). For patients who discontinue PALFORZIA treatment during the first year before their ps-IgE returns to pre-treatment levels, ps-IgE is expected to decrease over time without continuing exposure to peanut allergens. Given that the relative serum concentrations of IgE and IgG4 and the serum half-life of IgE (2 days; Lawrence, 2017) that is about one-tenth the serum half-life of IgG4 (21 days; Irani, 2015), a significant window of elevated ps-IgE and relatively low ps-IgG4 is unlikely and therefore any clinically detectable is not expected to occur.
Evidence source and strength of evidence	When PALFORZIA treatment is discontinued an increased severity of allergic reactions (ie, rebound) upon exposure to peanut could possibly occur compared with the severity of allergic reactions before or during treatment. However, this is very unlikely due to the competitive inhibition by IgG4 of antigen binding to IgE (Kulis, 2018; Vickery, 2013; Jones, 2009) and that the effects of IgE elevation have not been observed to result in rebound or exacerbated effects after discontinuation of treatment. For patients who discontinued the clinical studies early, no systemic allergic reaction events, accidental exposures to peanut, or other important safety events were reported in any of the follow-up periods. A search of the published literature found no reports that suggest an increased risk of increased severity of reactions (ie, rebound) following discontinuation of food OIT at any point during the process. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed for other OIT and the predicted mechanism.
Characterisation of the risk	A diligent search of the published literature was conducted, and no reports were found that suggest an increased risk of increased severity of reactions (ie, rebound) following discontinuation of food OIT at any point during the process. As such, the clinical development program was not structured to obtain data to support or negate this potential risk. Per protocols, subjects in PALFORZIA clinical studies were followed up for a short time after early treatment discontinuation (monitored for safety with assessments at the study site approximately 14 days after the last dose). Ongoing adverse events at discontinuation were monitored until the event resolved or was considered stable, or at least 30 days after the early discontinuation visit, whichever occurred first. These procedures represented additional safety measures to ensure that important medical events were followed up and not missed. Searching the clinical database confirmed that no systemic allergic reaction events, accidental exposures to peanut, or other important safety events were

Important Potential Risk 1: Possible rebound after discontinuation of treatment	
	reported in any study during this follow-up period. The MAH is not aware of any cases of rebound allergic reactions after discontinuation of treatment with PALFORZIA.
Risk factors and risk groups	There are no known risk factors that increase the risk of possible rebound after discontinuation of treatment. The risk factors that increase the likelihood of anaphylaxis/systemic allergic reactions are described for the important identified risk anaphylaxis/systemic allergic reactions.
Preventability	Healthcare professionals are advised in the PALFORZIA SmPC that stopping treatment will likely not maintain achieved efficacy. Patients must continue to carry self-injectable adrenaline at all times if treatment with PALFORZIA is stopped. Patients and caregivers are advised in the PL that stopping PALFORZIA may cause the patient to lose the built up peanut tolerance and increase the risk of allergic reactions.
Impact on the risk-benefit balance of the product	Possible rebound after discontinuation of treatment is currently a theoretical risk that is not supported by the immunomodulatory actions that occur. The effects of IgE elevation were not observed to result in rebound or exacerbated effects after discontinuation of treatment. There is no evidence from the follow-up of subjects who discontinued treatment in the clinical studies or from the published literature of an increased risk of increased severity of reactions (ie, rebound) following discontinuation of food OIT at any point during the process. Overall, the benefit of PALFORZIA as an effective OIT for desensitising peanut allergic patients and therefore decreasing the risk of life-threatening anaphylaxis outweighs the risk of possible rebound after discontinuation of treatment that has yet to be confirmed; such reactions, should they occur, can be managed in clinical practice through patient monitoring. Possible rebound after discontinuation of treatment will be further characterised in an open-label, longer-term follow-on study (ARC008[1]) that will evaluate safety data for patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation (Part III).
Public health impact	Overall, the public health impact of possible rebound after discontinuation of treatment is expected to be low given the expected reduction in anaphylaxis in peanut allergic patients treated with PALFORZIA.

[1]Study ARC008 is complete but as the CSR is currently under preparation it is still considered an ongoing study.

SVII.3.2. Presentation of the missing information

Missing Information 1: Use during pregnancy	
Evidence source	Patients who were pregnant were not treated with PALFORZIA in the clinical studies. Pregnancy PALFORZIA is associated with a risk of allergic reactions, including anaphylaxis, especially during initial dose escalation and up-dosing. Potential

Missing Information 1: Use during pregnancy	
	symptoms and signs of anaphylaxis and systemic allergic reactions in pregnancy include intense itching in the vulvar and vaginal areas, low back pain, uterine cramps, foetal distress, and preterm labour (Simons, 2012). 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 PALFORZIA on the immune system of the mother and foetus during pregnancy is unknown.
Population in need of further characterisation	There are no data on the use of PALFORZIA in pregnancy. No reports of pregnancy have been received during the post-marketing period up to the data lock point of 30 January 2024. <u>Pregnancy</u> Standard medical practice would dictate that immunotherapy would not be started or up-dosing of immunotherapy would not be continued in a pregnant woman. It is not expected, therefore, that a course of treatment with PALFORZIA would be started or that up-dosing would continue in a patient known to be pregnant, due to the potential for anaphylaxis/systemic allergic reactions. The PALFORZIA SmPC advises that initiation of PALFORZIA is not recommended during pregnancy. However, if a peanut-allergic patient is already tolerating maintenance dosing, then the risk of discontinuing desensitisation (allowing for re-sensitisation) may outweigh the risk of continuing treatment. This is because the risk of accidental peanut exposure may pose a greater risk of anaphylaxis than maintenance PALFORZIA. Therefore, healthcare professionals may elect to continue pregnant patients on PALFORZIA maintenance therapy based on the benefit-risk assessment for the individual. The PALFORZIA SmPC advises that for patients who are established on OIT therapy 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. Based on recent data in both animal models and humans, it is not expected that peanut consumption and by extension consumption of PALFORZIA, during pregnancy or lactation, will pose any safety concerns for the foetus or infant (Pitt, 2018; Maslova, 2012; López-Expósito, 2009). Because of the possibility that healthcare professionals may decide to continue maintenance therapy during pregnancy, a post-marketing pregnancy registry is collecting additional information on use of PALFORZIA in this population (Part III).

Missing Information 2: Impact on long-term immune-mediated reactions	
Evidence source	Longer-term safety data are available for 104 subjects and 26 subjects who completed 12 and 18 months respectively of maintenance treatment with 300 mg daily PALFORZIA in study ARC003 and the open-label, follow-on study ARC004. The impact on long-term immune-mediated reactions beyond this period are limited.

Missing Information 2: Impact on long-term immune-mediated reactions	
Population in need of further characterisation	Consistent with other desensitization treatments, it is expected that patients will stay on therapy for approximately 5 years. The impact on long-term immune-mediated reactions of PALFORZIA will be further characterised in an open-label, longer-term follow-on study (ARC008[1]) that will evaluate safety data for patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation (Part III).

[1]Study ARC008 is complete but as the CSR is currently under preparation it is still considered an ongoing study.

Part II: Module SVIII - Summary of the safety concerns

Table 18: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis
Important potential risks	Possible rebound after discontinuation of treatment
Missing information	Use during pregnancy Impact on long-term immune-mediated reactions

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires have been developed for the safety concerns (Annex 4):

- Anaphylaxis/systemic allergic reactions
- Eosinophilic oesophagitis

Other forms of routine pharmacovigilance activities for the safety concerns:

None

III.2 Additional pharmacovigilance activities

Study ARC008 is an ongoing, open-label, longer-term study designed to follow patients who have completed a prior PALFORZIA study (Annex 3). The CSR for Study ARC008 is currently under preparation. This study evaluated safety and tolerability, maintenance of desensitization, and effects on immunologic parameters in patients after longer-term administration of PALFORZIA (up to 5 years total treatment) with a subsequent 1-year follow-up observation after treatment discontinuation. During the observation period, patients were treated according to the recommendations of their treating healthcare professional. Therefore, patients may continue on commercially available PALFORZIA, use of food equivalents for peanut oral immunotherapy, or on peanut avoidance.

A post-marketing pregnancy registry is ongoing (Annex 3). The registry is operational in the US and in the EU. Annual reports are prepared and submitted with the periodic safety update reports (PSURs) following the data cut-off date.

Measures to evaluate the effectiveness of the additional risk minimisation measures, specifically the educational materials, have been developed (Annex 3).

Study short name and title:

Study ARC008: Open-label extension for maintenance of desensitization and safety

A multicentre, open-label, longer-term study of PALFORZIA characterised oral desensitisation immunotherapy in subjects who participated in a prior PALFORZIA study.

Rationale and study objectives:

Additional data on maintenance of desensitization and safety on longer term treatment with PALFORZIA is needed.

The objectives of the study are to evaluate safety and tolerability, maintenance of desensitization, and effects on immunologic parameters after longer-term administration of PALFORZIA and follow-up observation after treatment discontinuation.

Study design:

ARC008 is an international, open-label, longer-term follow-on study for ARC002, ARC004, ARC005, ARC007, ARC010, ARC011, and any future clinical study of PALFORZIA that identifies ARC008 as a follow-on study option.

Subjects aged 4 years or older at study entry in the original study were encouraged to remain in the study until their total exposure to PALFORZIA is 5 years including the prior study. After completing PALFORZIA treatment or after discontinuation of PALFORZIA treatment for any reason, subjects were followed up for approximately 1 year.

At the end of PALFORZIA treatment, all subjects have biomarker assessments (skin prick test, peanut-specific immunoglobulin [Ig] E and IgG4), and a DBPCFC up to 2000 mg peanut protein (4043 mg cumulative) or placebo followed by a 12-month observation period. During observation, management of peanut allergy is guided by the subject's physician. Observation assessments are as follows:

- Telephone follow-up at 3, 6, and 9 months to inquire about the following:
  - Current treatment plan (eg, continued peanut avoidance, use of food equivalents for peanut oral immunotherapy, commercially available PALFORZIA)
  - Events of systemic allergic reactions, eosinophilic esophagitis (EoE), accidental and nonaccidental exposures to food allergens and their outcomes, use of epinephrine (adrenaline), hospitalizations (all causes), emergency department visits (all causes), and serious adverse events

The same inquiries were made at 12 months. In addition, biomarkers (skin prick test, peanut-specific IgE and IgG4) were assessed and an optional DBPCFC conducted before study exit at 12 months. The end of the study is defined as the last visit/assessment by the last subject (aged 4 years or older at study entry in the original study) who completes 5 years of treatment with PALFORZIA and the 1-year follow-up period.

Protocol amendment 6.0 modified the primary endpoint of this study to assess the safety and tolerability during longer term administration of PALFORZIA and follow-up observation after the last dose of PALFORZIA (5 years of PALFORZIA treatment in patients enrolled in any prior PALFORZIA clinical study, and a 1 year follow-up observation period after stopping PALFORZIA treatment).

Study population:

All subjects previously participated in an PALFORZIA clinical study that identified ARC008 as a follow-on study option. Because these patients have already been on PALFORZIA therapy, they form a sentinel cohort where safety signals may be seen ahead of post-marketing data.

Milestones:

Protocol amendment 6 dated 22 December 2020 was submitted and approved in all countries where ARC008 is ongoing; a study synopsis is provided in **Erreur ! Source du renvoi introuvable.**.

Last patient last visit: 18 April 2023

Study end date: Q3 2023

Clinical Study Report (CSR): 16 Apr 2024

Registry name and title:

Post-marketing pregnancy registry

Rationale and registry objectives:

To collect, analyse, and report data on pregnancy outcomes and infant outcomes after exposure to PALFORZIA during pregnancy.

Registry design:

The pregnancy registry will collect, analyse, and report data on pregnancy outcomes and infant outcomes after exposure to PALFORZIA during pregnancy. In particular, the following outcomes will be examined:

- Episodes of anaphylaxis during pregnancy, whether the patient is on PALFORZIA or discontinued.
- Outcome of the pregnancy (ie, term delivery, premature delivery, type of delivery, spontaneous abortion, foetal deaths).
- Infant outcome at birth.

Events of anaphylaxis during pregnancy will be specifically collected even if the drug has been discontinued. By prospectively collecting this data, it may be possible to ascertain the rates of anaphylaxis for those women who discontinue or those who remain on PALFORZIA.

An annual cumulative report will be prepared. This report will be sent to regulators and will also be made available to healthcare professionals who are treating/advising women exposed during pregnancy to help inform their decision-making.

Population:

Women exposed to PALFORZIA within 2 weeks prior to last menstrual period or anytime during pregnancy.

Milestones:

Protocol version 0.0 dated 24 February 2020 (provided in RMP version 0.5).

Protocol amendment 1.0 dated 16 March 2021 (provided in **Erreur ! Source du renvoi introuvable.**).

Annual registry reports with data cut-off dates based on the international birthdate (IBD) are submitted with the periodic safety update reports (PSUR).

1st annual registry report (31-Jan-2020 to 30-Jan-2021) was submitted in October 2021 with 2nd PSUR (covering period 31-Jan-2021 to 30-Jul-2021).

2nd annual registry report (31-Jan-2021 to 30-Jan-2022) will be submitted in October 2022 with 4th PSUR (covering period 31-Jan-2022 to 30-Jul-2022).

Final study report: June 2025

Study short name and title:

Effectiveness evaluation of PALFORZIA educational materials

Rationale and study objectives:

The key study objectives are to evaluate:

- Healthcare professional's understanding and retention of core educational material messages
- Parent/caregiver's (1-3 year-old patients) understanding and retention of core educational messages
- Parent/caregiver's (4-11 year-old patients) understanding and retention of core educational messages
- Patient's (12-17 years old) understanding and retention of core educational messages
- Monitor adherence to educational materials distribution plan

Study design:

This is a post-authorisation cross-sectional descriptive survey study intended to be conducted in the EEA, UK, and Switzerland, with data collected systematically in specific countries when access to PALFORZIA becomes commercially available. After receiving PALFORZIA educational materials distributed according to a defined distribution plan, PALFORZIA prescribing HCPs, parents/caregivers of 1-3 year-old patients who have been prescribed PALFORZIA, parents/caregivers of 4-11 year-old patients who have been prescribed PALFORZIA, and 12-17 year-old patients who have been prescribed PALFORZIA, who provide informed consent, will complete an online survey in their local language. Data collection in each country will continue until completed, valid surveys are received from minimum desired sample size of 2 to 5 HCPs (depending on country size), 2 to 5 parents/caregivers of 1-3 year-old patients per HCP, 5 parents/caregivers of 4-11 year-old patients per HCP, and 5 patients aged 12-17 years per HCP, in each country.

Educational endpoints:

The study will evaluate whether the target of 80% correct responses on questions designed to assess key messages in the following domains was achieved:

- What is PALFORZIA and who should take it
- How is PALFORZIA to be administered
- What are the important risks for PALFORZIA, including recognition and treatment
- Importance of self-injectable adrenaline and understanding its use

Process indicator endpoints:

The study will evaluate whether the following endpoints were achieved:

- 100% adherence with distribution plan to health care providers
- HCPs supplied with a sufficient supply of patient cards for 100% of patients treated

Study population:

In each country of launch healthcare professionals (n = 2 to 5 depending on country size), 2 to 5 parents/caregivers of 1-3 year-old patients per HCP, 5 parent/caregivers (for 4-11 year-old patients) per HCP, and 5 patients (12-17 years old) per HCP who receive the educational

materials in the local language from start of the study will be offered the survey until the sample sizes are met for each country/language.

Milestones:

Planned start of data collection: June 2022

Final study report: June 2027

A study synopsis is provided in Annex 3. This will be updated to include parents/caregivers of 1-3 year-old patients leading to an expected extension to the study completion by 18 months.

III.3 Summary Table of additional Pharmacovigilance activities

Table 19: Ongoing and planned additional pharmacovigilance activities

Study name **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Open-label extension for maintenance of desensitization and safety (ARC008) Ongoing	To evaluate safety and tolerability, maintenance of desensitization, and effects on immunologic parameters after longer-term administration of PALFORZIA and follow-up observation after treatment discontinuation	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis Possible rebound after discontinuation of treatment Impact on long-term immune-mediated reactions	Protocol amendment 6	Dated 22 December 2020
			Last patient last visit	18 April 2023
			Study end date	Q3 2023
			CSR	16 Apr 2024
Post-marketing pregnancy registry	To monitor pregnancy outcomes in pregnant women exposed to PALFORZIA	Use during pregnancy	Protocol version 0.0	Dated 24 February 2020
			Protocol amendment 1.0	Dated 16 March 2021

Study name Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing in US and EU	ascertained by spontaneous reporting		Annual registry reports	The data lock is based on the IBD and submission coincides with the PSUR cycle
			1st annual registry report	October 2021 with 2nd PSUR
			2nd annual registry report	October 2022 with 4th PSUR
			Final study report	June 2025
Effectiveness evaluation of PALFORZIA educational materials Planned	The key study objectives are to evaluate: • Healthcare professional's understanding and retention of core educational material messages • Parent/caregiver's (1-3 year-old patients) understanding and retention of core educational messages • Parent/caregiver's (4-11 year-old patients) understanding and retention of core educational messages • Patient's (12-17 years old) understanding and retention of core educational messages • Monitor adherence to educational materials distribution plan	Anaphylaxis/ systemic allergic reactions Eosinophilic oesophagitis	Planned start of data collection	June 2022
			Final study report	June 2027

Part IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing imposed post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 20: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Anaphylaxis/systemic allergic reactions (Important identified risk)	Routine risk communication: • *Anaphylactic reaction, severe (anaphylaxis; systemic allergic reaction severe) and anaphylactic reaction (systemic allergic reaction; any severity) listed as adverse reactions in section 4.8 of the SmPC* • *Description of severe allergic reactions as a side effect in section 4 of the PL* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Contraindication for use in patients who had severe or life-threatening anaphylaxis within 60 days before initiating treatment in section 4.3 of the SmPC and section 2 of the PL* • *Warning of anaphylaxis/systemic allergic reactions addressed in section 4.4 of the SmPC and section 2 of the PL. Includes guidance regarding when to seek medical attention for signs or symptoms of allergic reactions* • *Guidance that self-injectable adrenaline must be prescribed to all patients in section 4.2 of the SmPC, section 4.4 of the SmPC, and section 2 of the PL* • *Guidance on management of co-factors including modifiable co-factors (hot bath or shower, exercise, fasting or empty stomach, alcohol (including medicinal products that contain alcohol), intake of non-steroidal anti-inflammatory medicines) and non-modifiable co-factors (intercurrent illness, exacerbation of asthma, menstruation, stress, fatigue or sleep deprivation) in section 4.4 of the SmPC and section 2 of the PL* • *Warning that PALFORZIA may not be suitable for patients taking medications that can inhibit or potentiate the effect of adrenaline and to refer to the SmPC for adrenaline for further information in section 4.5 of the SmPC with guidance to refer to the adrenaline PL about its use in section 2 of the PL* • *Guidance that the initial dose escalation, first dose of each new up-dosing level and first dose of maintenance are to be administered under the supervision of a healthcare professional qualified in diagnosis and treatment of allergic diseases in a healthcare setting prepared to manage severe allergic reactions in section 4.2 of the SmPC with similar guidance in section 3 of the PL* • *Guidance that care should be taken to ensure that patients only have one dose level in their possession at any time in section 4.2 of the SmPC* Other routine risk minimisation measures beyond the Product Information: • *Different dose levels distinguished through limiting the pack size and use of different coloured capsules or sachets. During up-dosing, first daily dose*

	will be given in a clinical setting. Complete daily dose is packaged in a 2-week pack with doses separated out and labelled by day for home use. The 300 mg dose for up-dosing is provided in sachets in a 15-dose pack. For maintenance dosing, each 300 mg dose is provided in an individual sachet, with home doses provided in packs of 30. PALFORZIA is available by prescription only.
Eosinophilic oesophagitis (EoE) (Important identified risk)	Routine risk communication: • *EoE listed as an adverse reaction in section 4.8 of the SmPC* • *Description of EoE as a side effect in section 4 of the PL* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Contraindication for patients with a history of, or current, EoE; other eosinophilic gastrointestinal disease; chronic, recurrent, or severe GERD; or dysphagia in section 4.3 of the SmPC with similar guidance for patients with, or who have previously had, a problem swallowing or long term problems with their digestive system in section 2 of the PL* • *Warning that EoE has been reported with PALFORZIA and to discontinue PALFORZIA and consider a diagnosis of EoE in patients who experience severe or persistent gastrointestinal symptoms including dysphagia, gastroesophageal reflux, chest pain or abdominal pain in section 4.4 of the SmPC* • *Warning to consider chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups or food refusal and failure to thrive in toddlers and younger patients (ages 1 to 3 years) for a potential diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE in section 4.4 of the SmPC* • *Warning for the patient to stop taking PALFORZIA and to get medical treatment straight away if they experience severe stomach cramps or pain, vomiting or diarrhoea in section 2 of the PL* Other routine risk minimisation measures beyond the Product Information: • *None*
Possible rebound after discontinuation of treatment (Important potential risk)	Routine risk communication: • *Information that stopping treatment will likely not maintain achieved efficacy in section 4.2 of the SmPC* • *Guidance that stopping PALFORZIA may cause the patient to lose the built up peanut tolerance and increase the risk of allergic reactions in section 3 of the PL* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Guidance that patients must continue to carry self-injectable adrenaline at all times if treatment with PALFORZIA is stopped in section 4.2 of the SmPC.* Other routine risk minimisation measures beyond the Product Information: • *None*

Use during pregnancy (Missing information)	Routine risk communication: • *Statement that there are no data on the clinical experience of PALFORZIA in pregnant women in section 4.6 of the SmPC* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Warning that PALFORZIA should not be initiated during pregnancy in section 4.6 of the SmPC.* • *Guidance for the patient not to start treatment with PALFORZIA if she is pregnant or planning to become pregnant and to ask her doctor for advice in section 2 of the PL* • *Guidance for a benefit/risk assessment to be undertaken for patients established on OIT therapy and who become pregnant considering the benefits of OIT and retaining desensitisation and the risks of an anaphylactic reaction while remaining on OIT in section 4.6 of the SmPC* Other routine risk minimisation measures beyond the Product Information: • *None*
Impact on long-term immune-mediated reactions	Routine risk communication: • *Information that efficacy data are available for PALFORZIA treatment in patients ages 4 to 17 years for up to 24 months and that no recommendation can be made about the duration of treatment beyond 24 months in section 4.2 of the SmPC* • *Information that efficacy data are available for PALFORZIA treatment in patients ages 1 to 3 years for up to 12 months and that no recommendation can be made about the duration of treatment beyond 12 months in section 4.2 of the SmPC* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond the Product Information: • *None*

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1: Healthcare professional educational materials

Objectives:

To help educate and train healthcare professionals on the safe use of PALFORZIA. The MAH has developed educational materials for professional use consisting of a collection of print and on-line materials including an instruction manual that will provide guidance on PALFORZIA treatment and safety (Annex 6). These materials will include a description of adverse reactions, including the risks of anaphylaxis/systemic allergic reactions and EoE. The warnings and precautions for use of PALFORZIA will also be highlighted including the required prescription for epinephrine auto-injectors to all patients prescribed PALFORZIA. These materials in concert with the SmPC will encourage safe use of the product.

Rationale for the additional risk minimisation activity: PALFORZIA is a medication with a complex dosing regimen and the potential for significant adverse events. Educating healthcare professionals on patient selection, adverse reactions and their management, and appropriate patient monitoring can help minimise the risk to patients.

Target audience and planned distribution path: Healthcare professionals prescribing PALFORZIA.

Plans to evaluate the effectiveness of the healthcare professional educational materials: The key objectives are understanding and retention of the core educational material messages by healthcare professionals and patients and monitoring of adherence to the educational material distribution plan.

To assess the effectiveness of the educational materials, a structured survey has been developed and will be made available to healthcare professionals to assess the effectiveness of their respective PALFORZIA educational materials (Part III.2; Annex 3).

The surveys will be hosted online and will evaluate the following for healthcare professionals:

- Healthcare professional's understanding and retention of core educational material messages
- Monitor adherence to educational materials distribution plan

The criteria for success will be determined based on educational endpoints and process indicator endpoints.

Educational Endpoints:

Achieve a target of 80% correct responses on questions designed to assess key messages in the following domains:

- What is PALFORZIA and who should take it
- How is PALFORZIA to be administered
- What are the important risks for PALFORZIA, including recognition and treatment
- Importance of self-injectable adrenaline and understanding its use

Process indicator endpoints:

- 100% adherence with distribution plan to health care providers
- HCPs supplied with a sufficient supply of patient cards for 100% of patients treated

Educational materials will be re-evaluated in light of the results of the effectiveness study, if required.

Safety monitoring for the key identified risks will be undertaken as part of routine pharmacovigilance and outcomes reported via the periodic safety reports. A comprehensive pharmacovigilance questionnaire has been developed for use for all cases of anaphylaxis spontaneously reported to the MAH (Part III.1; Annex 4). The purpose of this questionnaire is to aid in the collection of standardised and complete data on these cases of anaphylaxis. The MAH will analyse the reported cases of anaphylaxis for each PSUR, and the analysis will be part of the periodic report to the agency. Should safety monitoring indicate that there is a concerning rate of occurrence of adverse events that were addressed or could be addressed in these materials, the materials will be reassessed.

Additional risk minimisation 2: Patient and parent/caregiver educational materials

Objectives:

To help to educate patients and/or their parents/caregivers on the risks associated with PALFORZIA including anaphylaxis/systemic allergic reactions and EoE, how to use PALFORZIA safely, and when to contact their healthcare professional. Safety monitoring for the key identified risks will be undertaken as part of routine pharmacovigilance and outcomes reported via the periodic safety reports.

These materials consisting of a collection of print and on-line materials and patient video resources will help the healthcare professional to counsel patients as they start therapy with PALFORZIA. These materials have been developed in lay terms to an appropriate reading age for the following audiences: patients aged 4 to 6, 7 to 11 and 12 to 17 years old, and parents/caregivers. The materials provide guidance on PALFORZIA treatment and safety (Annex 6).

The materials in use for children aged 4 to 6 years old will be modified to be more broadly applicable also for use in toddlers aged 1 to 3 years. The expectation is that parents/caregivers will read the printed materials to patients aged 1 to 3 years. Printed educational materials will be updated to align the introductory pages targeted to the parent/caregiver of the child as needed and the title page will be updated to reflect the broader use of the booklet in patients aged 1 to 6 years. No new educational materials will be developed specifically for use in toddlers aged 1 to 3 years.

A Patient Card for the patient to carry will inform healthcare personnel should emergency care be needed in the case of anaphylaxis/systemic allergic reactions (Annex 6).

These materials in concert with the PL will encourage safe use of the product.

Rationale for the additional risk minimisation activity: PALFORZIA is a medication with a complex regimen and the potential for significant adverse events. Patients and/or their parents/caregivers will require education and counselling regarding the appropriate use, adverse reactions and their management, and when to seek medical care. Educating patients and/or their parents/caregivers will help minimise the risk of anaphylaxis/systemic allergic reactions and EoE to patients.

Target audience and planned distribution path: Patients treated with PALFORZIA and/or their parents/caregivers. The Patient Card will be distributed to the patient/caregiver by the prescriber who will be supplied with sufficient cards for their patients.

Plans to evaluate the effectiveness of the patient and parent/caregiver educational materials: The key objectives are understanding and retention of the core educational material messages by patients and parents/caregivers.

To assess the effectiveness of the educational materials, a structured survey has been developed and will be made available to parents/caregivers and patients to assess the effectiveness of their respective PALFORZIA educational materials (Part III.2; Annex 3).

The surveys will be hosted online and will evaluate the following:

- Healthcare professional's understanding and retention of core educational material messages
- Parent/caregiver's (1-3 year-old patients) understanding and retention of core educational messages
- Parent/caregiver's (4-11 year-old patients) understanding and retention of core educational messages
- Patient's (12-17 years old) understanding and retention of core educational messages

The criteria for success will be determined based on educational endpoints and process indicator endpoints.

Educational Endpoints:

Achieve a target of 80% correct responses on questions designed to assess key messages in the following domains:

- What is PALFORZIA and who should take it
- How is PALFORZIA to be administered
- What are the important risks for PALFORZIA, including recognition and treatment
- Importance of self-injectable adrenaline and understanding its use

A study synopsis is provided in Annex 3. This will be updated to include parents/caregivers of 1-3 year-old patients leading to an expected extension to the study completion by 18 months.

Educational materials will be re-evaluated in light of the results of the effectiveness study, if required.

Safety monitoring for the key identified risks will be undertaken as part of routine pharmacovigilance and outcomes reported via the periodic safety reports. A comprehensive pharmacovigilance questionnaire has been developed for use for all cases of anaphylaxis spontaneously reported to the MAH (Part III.1; Annex 4). The purpose of this questionnaire is to aid in the collection of standardised and complete data on these cases of anaphylaxis. The MAH will analyse the reported cases of anaphylaxis for each PSUR, and the analysis will be part of the periodic report to the agency. Should safety monitoring indicate that there is a concerning rate of occurrence of adverse events that were addressed or could be addressed in these materials, the materials will be reassessed.

Removal of additional risk minimisation activities

Not applicable

V.3 Summary of risk minimisation measures

Table 21: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anaphylaxis/systemic allergic reactions (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.2, SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8* • *PL section 2, PL section 3, and PL section 4* • *Different dose levels distinguished through limiting the pack size and use of different coloured capsules* • *Prescription only medicine* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials and Patient Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *AE follow-up questionnaire for adverse reaction* Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials*
Eosinophilic oesophagitis (EoE) (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8* • *PL section 2 and PL section 4* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *AE follow-up questionnaire for adverse reaction* Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials*
Possible rebound after discontinuation of treatment (Important potential risk)	Routine risk minimisation measures: • *SmPC section 4.2* • *PL section 3* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study ARC008 extension*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use during pregnancy (Missing information)	Routine risk minimisation measures: • *SmPC section 4.6* • *PL section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Post-marketing pregnancy registry*
Impact on long-term immune-mediated reactions (Missing information)	Routine risk minimisation measures: • *SmPC section 4.2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study ARC008 extension*

Part VI: Summary of the risk management plan

Summary of risk management plan for PALFORZIA (defatted powder of *Arachis hypogaea L.*, semen (peanuts))

This is a summary of the risk management plan (RMP) for PALFORZIA. The RMP details important risks of PALFORZIA, how these risks can be minimised, and how more information will be obtained about PALFORZIA's risks and uncertainties (missing information).

PALFORZIA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PALFORZIA should be used.

This summary of the RMP for PALFORZIA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of PALFORZIA's RMP.

I. The medicine and what it is used for

PALFORZIA is authorised for patients aged 1 to 17 years of age with a confirmed peanut allergy and may be continued in patients 18 years of age and older (see SmPC for the full indication). It contains defatted powder of *Arachis hypogaea* L., semen (peanuts) as the active substance, and it is taken orally.

Further information about the evaluation of the benefit of PALFORZIA can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/palforzia.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PALFORZIA, together with measures to minimise such risks and the proposed studies for learning more about risks with PALFORZIA, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of PALFORZIA, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment – so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of PALFORZIA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of PALFORZIA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PALFORZIA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis
Important potential risks	Possible rebound after discontinuation of treatment
Missing information	Use during pregnancy Impact on long-term immune-mediated reactions

II.B Summary of important risks

Important identified risk: Anaphylaxis/systemic allergic reactions	
Evidence for linking the risk to the medicine	Patients with peanut allergy may have allergic symptoms, including systemic allergic reactions, when treated with PALFORZIA as it contains defatted powder of *Arachis hypogaea L.*, semen (peanuts). *Systemic allergic reaction* is used to describe an anaphylactic reaction of any severity and *anaphylaxis* is used to describe an anaphylactic reaction events that is severe. In the integrated safety population that evaluated PALFORZIA treatment in subjects aged 4 to 17 years, systemic allergic reactions of any severity were reported in 15.8% of subjects, including 0.6% during initial dose escalation, 8.7% during up-dosing and 10.5% during maintenance. Severe systemic allergic reaction (anaphylaxis) was reported in 1.1% subjects, including 0.4% subjects during up-dosing and 0.8% during maintenance at 300 mg/day. In study ARC005 that evaluated PALFORZIA treatment in subjects aged 1 to 3 years, systemic allergic reactions of any severity were reported in 8.2% of subjects treated with PALFORZIA, including 2.0% during up-dosing and 6.9% during maintenance. Systemic allergic reactions of any severity occurred in 8.3% of placebo treated subjects including 4.2% during up-dosing and 4.4% during

	maintenance. No severe or serious systemic allergic reactions occurred in either group. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Patients are more likely to experience allergic symptoms in the presence of certain co-factors which are known to increase the likelihood of allergic reactions in general. These cofactors may be modifiable or non-modifiable. Modifiable co-factors may include exercise, hot bath or shower, alcohol consumption, fasting, or intake of non-steroidal anti-inflammatory medications. Non-modifiable co-factors may include intercurrent illness (eg, influenza or viral infection), an increase in severity of asthma, menstruation, stress, fatigue or sleep deprivation (Smith, 2015; Turner, 2017b; Varshney, 2009). In addition, patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2, SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8* • *PL section 2, PL section 3, and PL section 4* • *Different dose levels distinguished through limiting the pack size and use of different coloured capsules* • *Prescription only medicine* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials and Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Eosinophilic oesophagitis (EoE)	
Evidence for linking the risk to the medicine	Eosinophilic oesophagitis is a significant allergic condition which if left untreated can cause lasting damage to the oesophagus. EoE has been reported for other OIT used to treat food allergies. In the integrated safety population, EoE was diagnosed in 5 of 944 subjects (0.5%) with a further 7 cases in other studies (1 subject in ARC001, 1 subject in ARC002, 1 subject in ARC004, and 4 subjects in ARC008) to total 12 of 1217 subjects (approximately 1%) treated with PALFORZIA experiencing EoE. After PALFORZIA was discontinued symptoms were considered recovered/resolved or recovering/resolving in all 12 subjects. In study ARC005, no subject was diagnosed with EoE. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a

	possible causal association based on what has been observed for other OIT and the predicted mechanism.
Risk factors and risk groups	A strong association between IgE-mediated food allergy and EoE has been observed (Greenhawt, 2014; Spergel, 2012). Consequently, patients with IgE-mediated food allergy who encounter the food to which they are allergic, either naturally or during OIT, are at increased risk of EoE. It remains unclear whether OIT induces EoE or causes pre-existing subclinical EoE to become symptomatic (Wright, 2018). The aetiology of EoE is multifactorial and unlike food anaphylaxis, which occurs in an estimated 15% of EoE patients (Assa'ad, 2007), patients with EoE are polysensitised to a variety of foods suggesting a general breakdown in oral antigen tolerance (Rothenberg, 2009). Male sex is a strong risk factor for EoE both in children and adults (Arias, 2016). Eosinophilic oesophagitis may occur at any age but there is a rising incidence in children with age and a peak in adults at 30-50 years with most cases occurring in children, adolescents, and adults younger than 50 years (Lucendo, 2017). A retrospective database analysis over a period of 8 years found that in 89 paediatric patients with EoE up to 18 years of age, male sex (78.6%), white race (94.4%), young age at diagnosis (mean ± SD, 6.2 ± 4.8 years), and atopy with sensitisation to environmental and food allergens in 79% and 75%, respectively, were prevalent (Assa'ad, 2007). The associated conditions extracted from the past medical history of the 89 patients or reported by the parents were atopy (asthma, allergic rhinitis, eczema, anaphylaxis to food, and allergic conjunctivitis in 39%, 30%, 19%, 9%, and 8%, respectively); immunologic (recurrent infections and autoimmune disorders in 13% and 2%, respectively); and developmental and neurologic (developmental delay, seizures, cerebral palsy, autism in 12%, 6%, 4%, and 1%); and chromosomal abnormalities in 1% patients (Assa'ad, 2007). EoE patients usually suffer from a high number of concomitant atopic disorders including rhinitis, asthma and eczema. A recent systematic review of 21 studies comprising 53,542 EoE patients and 54,759 controls found that allergic rhinitis was significantly more common among patients with EoE compared with control subjects as were bronchial asthma and eczema (González-Cervera, 2017). Eosinophilic oesophagitis has a strong familial association (Rothenberg, 2009). Nearly 10% of parents of EoE patients have a history of oesophageal strictures and an estimated 8% have biopsy proven EoE (Noel, 2004). In a study out of the 103 paediatric patients 73.5% had a family history of atopic disease, 6.8% a family history of EoE, 9.7% a family history of oesophageal dilatation, 57.4% rhinoconjunctivitis, 36.8% wheezing, and 46% possible food allergy (Noel, 2004).
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.3*, *SmPC section 4.4*, *and SmPC section 4.8* • *PL section 2 and PL section 4* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials*

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Possible rebound after discontinuation of treatment	
Evidence for linking the risk to the medicine	When PALFORZIA treatment is discontinued an increased severity of allergic reactions (ie, rebound) upon exposure to peanut could possibly occur compared with the severity of allergic reactions before or during treatment. However, this is very unlikely due to the competitive inhibition by IgG4 of antigen binding to IgE (Kulis, 2018; Vickery, 2013; Jones, 2009) and that the effects of IgE elevation have not been observed to result in rebound or exacerbated effects after discontinuation of treatment. For patients who discontinued the clinical studies early, no systemic allergic reaction events, accidental exposures to peanut, or other important safety events were reported in any of the follow-up periods. A search of the published literature found no reports that suggest an increased risk of increased severity of reactions (ie, rebound) following discontinuation of food OIT at any point during the process. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed for other OIT and the predicted mechanism.
Risk factors and risk groups	There are no known risk factors that increase possible rebound after discontinuation of treatment. The risk factors that increase the likelihood of anaphylaxis/ systemic allergic reactions are described for the important identified risk anaphylaxis/systemic allergic reactions.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2* • *PL section 3* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use during pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.6* • *PL section 2* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Post-marketing pregnancy registry* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Impact on long-term immune-mediated reactions	
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PALFORZIA.

II.C.2 Other studies in post-authorisation development plan

Study ARC008: Open-label extension for maintenance of desensitization and safety

Purpose of the study: Additional data on maintenance of desensitization and safety on longer-term treatment with PALFORZIA is needed.

The objectives of the study are to evaluate safety and tolerability, maintenance of desensitization, and effects on immunologic parameters after longer-term administration of PALFORZIA and follow-up observation after treatment discontinuation.

Post-marketing pregnancy registry

Purpose of the study: To collect, analyse, and report data on pregnancy outcomes and infant outcomes after exposure to PALFORZIA during pregnancy.

Effectiveness evaluation of PALFORZIA educational materials

Purpose of the study: The key study objectives are to evaluate:

- Healthcare professional's understanding and retention of core educational material messages
- Parent/caregiver's (1-3 year-old patients) understanding and retention of core educational messages
- Parent/caregiver's (4-11 year-old patients) understanding and retention of core educational messages
- Patient's (12-17 years old) understanding and retention of core educational messages
- Monitor adherence to educational materials distribution plan

Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract. 2017 Sep-Oct;5(5):1169-1178. Vickery BP, Lin J, Kulis M, Zhiyan F, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013;131(1):128-34.

Part VII: Annexes

Annex 1 – Specific adverse drug reaction follow-up forms

Table of contents

Case Reference No._____
Date of Receipt (DDMMMYYYY)_____

PALFORZIA™ Anaphylaxis Questionnaire Health Care Professional

Complete this form in addition to the regular AE report form for all reports of anaphylaxis, severe allergic reactions, systemic allergic reactions.

Adverse Event Characteristics		
Time from most recent dose of PALFORZIA™ to first symptom onset: hours minutes		
Other suspect allergens:		
Please check all that apply: ☐ Sudden Onset ☐ Rapid progression of signs/symptoms		
Check all criteria listed below that apply to the Adverse Event		
Body System	**Major Criteria**	**Minor Criteria**
Dermatological or mucosal	☐ generalized urticaria (hives) ☐ generalized erythema ☐ angioedema (localized or generalized) ☐ generalized pruritis with skin rash	☐ generalized pruritis without skin rash ☐ generalized prickle sensation ☐ red, itchy eyes
Cardiovascular	☐ measured hypotension: systolic_____diastolic_____mmHg ☐ uncompensated shock as evidenced by ≥ 3 of the following: ☐ tachycardia: _____ bpm ☐ capillary refill time > 3 seconds (s) ☐ reduced central pulse volume ☐ decreased level or loss of consciousness	☐ reduced peripheral circulation as indicated by 2 of the following: ☐ tachycardia: _____ bpm ☐ capillary refill time > 3 s, without hypotension ☐ decreased level of consciousness
Respiratory	☐ bilateral wheeze (bronchospasm) ☐ stridor ☐ upper airway swelling, check all that apply: ☐ lip ☐ tongue ☐ throat ☐ uvula ☐ larynx ☐ respiratory distress with ≥ 2 of the following: ☐ tachypnea: _____ breaths pm ☐ increased use of accessory muscles ☐ recession ☐ cyanosis ☐ grunting	☐ persistent dry cough ☐ hoarse voice ☐ difficulty breathing without wheeze or stridor ☐ sensation of throat closure ☐ sneezing, rhinorrhea
Gastrointestinal	NA	☐ diarrhea ☐ abdominal pain ☐ nausea ☐ vomiting
Laboratory	NA	☐ mast cell tryptase elevated above ULN*

*Upper limit of normal
Note: these criteria will be analyzed using the Brighton case definition for anaphylaxis

Case Reference No._____
Date of Receipt (DDMMMYYYY)_____

PALFORZIA™ Anaphylaxis Questionnaire Health Care Professional

Enter all forms of treatment administered including brand name if known (e.g. antihistamines, steroids, etc.)		
Adverse Event Treatment	**Dosing**	**Number of Doses**
Epinephrine		

Was epinephrine immediately available on-site at the time of the anaphylactic reaction? ☐ Yes ☐ No If No, please describe why epinephrine was not available.

While the cofactors listed below may or may not apply to your patient, with respect to the Adverse Event the patient experienced, enter a check in the columns next to the cofactors below.				
Cofactors	**Yes**	**No**	**Unk**	**NA**
Physical exertion shortly before dose administration				
Currently taking NSAIDS (e.g. aspirin, ibuprofen, naproxen)				
Alcohol intake within 2 hours before or after dose administration				
If female, was the patient menstruating? Date of Last Menstrual Period (DDMMMYYYY): _____				
Did the patient experience a risk factor for increased body temperature (e.g. hot shower/bath, hot tub use) near time of dose administration				
Was the patient sleep deprived or have excessive fatigue the day of the event?				
Was the dose administered with sufficient food intake (i.e. following a large snack or meal)?				
Was there an error or irregularity in the preparation/mixing of the dose in the food vehicle?				

Were symptoms of an allergic comorbidity (e.g. allergic rhinitis, atopic dermatitis, asthma) noted at time of event? ☐ Yes ☐ No If yes describe below.

Were other co-factors not noted/ not listed above, present which may have decreased the patient's threshold for anaphylaxis? ☐ Yes ☐ No If yes describe below.

Name: Signature:	Date:

Case Reference No._____
Date of Receipt (DDMMMYYYY)_____

PALFORZIA™ Eosinophilic Esophagitis Questionnaire Health Care Professional

Complete this form in addition to the regular AE report form for all reports of eosinophilic esophagitis (EOE).

Indicate if you have had the past medical condition listed below or have a concurrent illness by indicating in the comment column. Check all that apply.

Medical Condition	**Yes**	**No**	**Past or Concurrent (enter number)** **1. Past** **2. Concurrent**	**Comment**
Achalasia	☐	☐		
Allergic rhinitis	☐	☐		specify allergen:
Asthma	☐	☐		
Celiac disease	☐	☐		
Crohn's disease	☐	☐		
Eczema/atopic dermatitis	☐	☐		
Food allergies	☐	☐		specify
Gastroesophageal reflux disease (GERD)	☐	☐		

Indicate if you have experienced the symptoms related to eosinophilic esophagitis listed below. Check all that apply and complete the columns to the right.

Symptom	**Onset Date (DDMMMYYYY)**	**Resolution Date (DDMMMYYYY)**	**Outcome (enter number)** **1. Improved** **2. Recovered** **3. Recovered with sequelae** **4. Not Recovered**	**Present prior to PALFORZIA administration? (enter number)** **1. Yes** **2. No**
☐ Abdominal pain				
☐ Chest pain				
☐ Difficult or painful swallowing				
☐ Failure to thrive				
☐ Feeding difficulties				
☐ Food impaction				
☐ Nausea				
☐ Reflux/heartburn				
☐ Regurgitation				
☐ Vomiting				

Case Reference No._____
Date of Receipt (DDMMMYYYY)_____

Provide details for the procedures and/or laboratory exams performed, including the findings in the form of description or lab results. Populate additional rows if more procedures or laboratory exams are performed.

Procedure/Laboratory Exam	**Date (DDMMMYYYY)**	**Findings**	**Results/Comments**
Endoscopy Initial		☐Gross abnormalities ☐ Esophageal Biopsy	Histology: Peak esophageal eos per hpf _____ ☐proximal ☐distal
Endoscopy Follow-up		☐Gross abnormalities ☐ Esophageal Biopsy	Histology: Peak esophageal eos per hpf _____ ☐proximal ☐distal
Blood eosinophil count		☐Total eosinophils ☐% eosinophils	
Blood eosinophil count		☐Total eosinophils ☐% eosinophils	

Case Reference No._____
Date of Receipt (DDMMMYYYY)_____

Indicate below the type of treatment administered and the details including duration of treatment				
Treatment	**Type**	**Dosage and Frequency**	**Start Date (DDMMMYYYY)**	**Stop Date (DDMMMYYYY)**
Proton Pump Inhibitors				
Systemic steroids				
Topical steroids				
Elimination diet				
Other				
Other				

Name: Signature:	Date:

Annex 2 – Details of proposed additional risk minimisation activities

Key messages of the additional risk minimisation measures

Healthcare professional educational materials:

The Summary of Product Characteristics

Healthcare professional educational materials:

These materials consist of print and on-line materials and video resources including an instruction manual. The instruction manual is a reference document which details the appropriate use of PALFORZIA and will include the following information:

- Treatment overview
    - Summary of relevant background information and overview of the three dosing phases (initial dose escalation, up-dosing and maintenance)
    - Explanation of dose preparation and administration
    - When to consider dose modifications and management of missed doses
- Safety overview
    - Summary of risks of anaphylaxis and eosinophilic oesophagitis with focus on the identification of symptoms, management, and mitigation of known risks (including – co-factors which may precipitate systemic allergic reactions)
    - Summary of common side effects with focus on severity, frequency, and management
    - Explanation of requisite treatment adherence with focus on daily dosing, peanut avoidance, and appropriate prescription and use of emergency adrenaline
    - Appropriate referral to SmPC for additional information
    - Country-specific guidance on how and when to report adverse events

Patient and parent/caregiver educational materials:

Package leaflet

Patient and parent/caregiver educational materials:

These consist of a collection of print and on-line materials and video resources that will be developed in lay terms to an appropriate reading age for the following audiences: patients aged 1–6, 7–11, and 12–17 years old, and parents/caregivers. Materials will include the following information:

- Treatment overview
    - Brief explanation as to what PALFORZIA is used for, which patients are suitable to be treated with PALFORZIA, and who should not take the medicine
    - Summary of relevant background information and overview of the three dosing phases (initial dose escalation, up-dosing, and maintenance)
    - How to safely prepare, administer, and (if necessary) store doses and dispose of unused doses
- Safety overview
    - Summary of risks of anaphylaxis and eosinophilic oesophagitis with focus on the identification of symptoms, management, and mitigation of known risks (including co-factors which may precipitate systemic allergic reactions)

- Summary of common side effects with focus on severity, frequency, and management
- Explanation of requisite treatment adherence with focus on daily dosing, peanut avoidance, and appropriate use of emergency adrenaline
- Appropriate referral to package leaflet for additional information
- Description of how and when to report side effects to a healthcare professional

Patient card

- To be given to a patient by the prescribing physician when PALFORZIA treatment is initiated
- Patients will be instructed to carry the card on their person at all times
- Warning for healthcare professionals treating the patient at any time, including in emergency situations, that the patient is peanut-allergic and that they are using PALFORZIA
- Warning that if anaphylaxis is suspected to administer a dose of adrenaline and to contact emergency services
- Description of the symptoms of anaphylaxis and when to contact a healthcare professional
- Emergency contact details for the patient
- Contact details of the PALFORZIA prescriber

Annex 3 – Other supporting data (including referenced material)

List of References

Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. J Allergy Clin Immunol. 2014;133(1):15664.

Altschul AS, Scherrer DL, Muñoz-Furlong A, Sicherer SH. Manufacturing and labeling issues for commercial products: relevance to food allergy. J Allergy Clin Immunol. 2001;108(3):468.

American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000;106(2 Pt 1):346-9.

Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297304.

Arias Á, Pérez-Martínez I, Tenías JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016 Jan;43(1):3-15.

Asai Y, Greenwood C, Hull PR, Alizadehfar R, Ben-Shoshan M, Brown SJ, et al. Filaggrin gene mutation associations with peanut allergy persist despite variations in peanut allergy diagnostic criteria or asthma status. J Allergy Clin Immunol. 2013 Jul;132(1):239-42.

Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. J Allergy Clin Immunol. 2007 Mar;119(3):731-8.

Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol. 2003;14(5):378-82.

Bégin P, Paradis L, Paradis J, Picard M, Des Roches A. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. J Allergy Clin Immunol Pract. 2013 Sep-Oct;1(5):528-30.e1-4.

Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol. 2007 Apr;119(4):1016-8.

Brough HA, Turner PJ, Wright T, Fox AT, Taylor SL, Warner JO, et al. Dietary management of peanut and tree nut allergy: what exactly should patients avoid? Clin Exp Allergy. 2015 May;45(5):859-871.

Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011 Mar;127(3):661-7.

Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. J Allergy Clin Immunol. 2008 Aug;122(2):286-9.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). Peanut allergy. London: Department of Health, 1998. /http://cot.food.gov.uk/pdfs/cotpeanutall.pdf.

Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010 Aug;65(8):933-45.

Deschildre A, Elegbédé CF, Just J, Bruyère O, Van der Brempt X, Papadopoulos A, et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. Clin Exp Allergy. 2016;46(4):61020.

Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008 Nov;122(5):984-91.

Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb 26;372(9):803-13.

Du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. J Allergy Clin Immunol. 2016;137:998–1010.

Ferro MA, Van Lieshout RJ, Ohayon J, Scott JG. Emotional and behavioral problems in adolescents and young adults with food allergy. Allergy. 2016 Apr;71(4):532-40.

Fischer D, Vander Leek TK, Ellis AK, Kim H. Anaphylaxis. Allergy Asthma Clin Immunol. 2018 Sep 12;14(Suppl 2):54.

Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. J Allergy Clin Immunol. 2003 Jul;112(1):183-9.

Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan ES, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. World Allergy Organ J. 2015 Aug 3;8(1):27.

Flokstra de Blok BM, Dubois AE, Vlieg Boerstra BJ, Oude Elberink JN, Raat H, DunnGalvin A, et al. Health related quality of life of food allergic patients: comparison with the general population and other diseases. Allergy. 2010;65(2):238-44.

Foong RX, du Toit G, Fox AT. Asthma, food allergy, and how they relate to each other. Front Pediatr. 2017 May 9;5:89.

Gillman A, Douglass JA. Asthma in the elderly. Asia Pac Allergy. 2012 Apr;2(2):101-8.

González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allergy Clin Immunol. 2010 May;125(5):1098-1104.

González-Cervera J, Arias Á, Redondo-González O, Cano-Mollinedo MM, Terreehorst I, Lucendo AJ. Association between atopic manifestations and eosinophilic esophagitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2017 May;118(5):582-590.e2.

Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. J Allergy Clin Immunol. 2016 Apr;137(4):1128-1137.

Greenhawt M, Aceves SS. Non-IgE medicated food allergy: eosinophilic esophagitis update on the pathogenesis, clinical features, and management of eosinophilic esophagitis in children. Curr Pediatr Rep. 2014;2(2):127-34.

Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011 Jul;128(1):e9-17.

Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018 Nov 19. pii: e20181235.

Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE-mediated food allergy. J Allergy Clin Immunol Pract. 2017;5(2):369-75.

Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic esophagitis is a late manifestation of the allergic march. J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1528-1533.

Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. J Allergy Clin Immunol. 2008 Mar;121(3):731-6.

Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. BMJ. 1996 Aug 31;313(7056):518-21.

Irani V, Guy AJ, Andrew D, Beeson JG, Ramsland PA, Richards JS. Molecular properties of human IgG subclasses and their implications for designing therapeutic monoclonal antibodies against infectious diseases. Molecular Immunology. 2015;67(2):171-82.

Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011 Oct 6;365(14):1315-27.

Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(2):292-300.

Joshi P, Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food allergic children. J Allergy Clin Immunol. 2002;109(6):1019-21.

King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. Allergy. 2009 Mar;64(3):461-8.

Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. J Allergy Clin Immunol. 2011 Mar;127(3):623-30.e1.

Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. J Allergy Clin Immunol. 2018;141(2):491-8.

Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008 Jun;121(6):1331-6.

Lawrence MG, Woodfolk JA, Schuyler AJ, Stillman LC, Chapman MD, Platts-Mills TA. Half-life of IgE in serum and skin: consequences for anti-IgE therapy in patients with allergic disease. J Allergy Clin Immunol. 2017;139(2):422-8.

Leickly FE, Kloepfer KM, Slaven JE, Vitalpur G. Peanut Allergy: An Epidemiologic Analysis of a Large Database. J Pediatr. 2018 Jan;192:223-228.

Leung DY. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. J Allergy Clin Immunol. 2009 Sep;124(3):494-5.

Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6; quiz 21-2.

Liem JJ, Huq S, Kozyrskyj AL, Becker AB. Should younger siblings of peanut-allergic children be assessed by an allergist before being fed peanut? Allergy Asthma Clin Immunol. 2008 Dec 15;4(4):144-9.

López-Expósito I, Song Y, Järvinen KM, Srivastava K, Li XM. Maternal peanut exposure during pregnancy and lactation reduces peanut allergy risk in offspring. J Allergy Clin Immunol. 2009 Nov;124(5):1039-46.

Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ, et al. Do boys do the atopic march while girls dawdle? J Allergy Clin Immunol. 2008 May;121(5):1190-5.

Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014 Dec;113(6):624-9.

Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017 Apr;5(3):335-358.

Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Arch Dis Child. 2002 Apr;86(4):236-9.

Marklund B, Wilde-Larsson B, Ahlstedt S, Nordström G. Adolescents' experiences of being food-hypersensitive: a qualitative study. BMC Nurs. 2007 Oct 9;6:8.

Maslova E, Granström C, Hansen S, Petersen SB, Strøm M, Willett WC, et al. Peanut and tree nut consumption during pregnancy and allergic disease in children-should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. J Allergy Clin Immunol. 2012 Sep;130(3):724-32.

Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. J Immunol. 2002 Mar 1;168(5):2464-9.

Mueller GA, Maleki SJ, Pedersen LC. The molecular basis of peanut allergy. Curr Allergy Asthma Rep. 2014 May;14(5):429.

Müller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. J Allergy Clin Immunol. 2001 Jan;107(1):81-6.

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69:1008-1025.

Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. Pediatr Allergy Immunol. 2012;23:133-9.

NICE guideline. Asthma: diagnosis, monitoring and chronic asthma management Published: 29 Nov 2017 nice.org.uk/guidance/ng80.

Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004 Aug 26;351(9):940-1.

Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007.

Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: IgE-mediated Food Allergy Allergy. 2017.

Papadopoulos A, Elegbede CF, Ait-Dahmane S, Dubuisson C, Deschildre A, Crépet A. Tree nut allergy and anxiety related factors modulate food consumption behaviour in peanut-allergic patients: Results of the MIRABEL survey. Regul Toxicol Pharmacol. 2018 Nov;99:191-199.

Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. J Allergy Clin Immunol. 2015 May;135(5):1257-66.e1-2.

Pitt TJ, Becker AB, Chan-Yeung M, Chan ES, Watson WTA, Chooniedass R, Azad MB. Reduced risk of peanut sensitisation following exposure through breast-feeding and early peanut introduction. J Allergy Clin Immunol. 2018 Feb;141(2):620-625.e1.

Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut allergic children. Clin Exp Allergy. 2000;30(8):1135-43.

Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol. 2007 Apr;119(4):1018-9.

Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol. 2012 Aug;26(8):1045-60.

Rothenberg ME. Biology and treatment of eosinophilic esophagitis. Gastroenterology. 2009 Oct;137(4):1238-49.

Sampson HA. Food allergy-accurately identifying clinical reactivity. Allergy. 2005;60 Suppl 79:19-24.

Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6.

Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Clin Immunol. 1999;103:559-62.

Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. J Allergy Clin Immunol. 2000 Jul;106(1 Pt 1):53-6.

Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;125:1322-6.

Simons FE. Anaphylaxis, killer allergy: long-term management in the community. J Allergy Clin Immunol. 2006 Feb;117(2):367-77.

Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011 Feb;4(2):13-37.

Simons FE, Schatz M. Anaphylaxis during pregnancy. J Allergy Clin Immunol. 2012 Sep;130(3):597-606.

Singh AM, Moore PE, Gern JE, Lemanske RF Jr, Hartert TV. Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation. Am J Respir Crit Care Med. 2007 Jan 15;175(2):108-19.

Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol. 2001;107(2):367-74.

Smith PK, Hourihane JO, Lieberman P. Risk multipliers for severe food anaphylaxis. World Allergy Organ J. 2015 Nov 24;8(1):30.

Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012;130(2):461-7.

Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Clin Exp Allergy. 2017 Jun;47(6):719-739.

Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clin Gastroenterol Hepatol. 2008 May;6(5):598-600.

Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, et al. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. J Allergy Clin Immunol. 2008 Mar;121(3):632-638.e2.

Thomsen SF. Epidemiology and natural history of atopic diseases. Eur Clin Respir J. 2015; 2: 10.3402/ecrj.v2.24642.

Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR Jr, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. Ann Allergy Asthma Immunol. 2017 Feb;118(2):166-173.e7.

Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135:956-63.

Turner PJ, Campbell DE. Implementing primary prevention for peanut allergy at a population level. JAMA. 2017;317(11):1111-1112. (Turner, 2017a)

Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract. 2017 Sep-Oct;5(5):1169-1178. (Turner, 2017b)

Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2013 Dec;43(12):1333-41.

Valent P, Akin C, Arock M. Diagnosis and treatment of anaphylaxis in patients with mastocytosis. Curr Treat Options Allergy 2014;1:247-261.

van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ. 2009 Jul 9;339:b2433.

Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr. 2000;137(6):749-55.

Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009 Dec;124(6):1351-2.

Vickery BP, Lin J, Kulis M, Zhiyan F, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013;131(1):128-34.

Vierk K, Falci K, Wolyniak C, Klontz KC. Recalls of foods containing undeclared allergens reported to the US Food and Drug Administration, fiscal year 1999. J Allergy Clin Immunol. 2002;109(6):1022-6.

Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007;119(6):1504-10.

Worm M, Scherer K, Köhli-Wiesner A, Ruëff F, Mahler V, Lange L, et al. Food-induced anaphylaxis and cofactors - data from the anaphylaxis registry. Allergol Select. 2017 Aug 4;1(1):21-27.

Wright BL, Rank MA, Shim KS, Doyle AD, Jacobsen EA, Manohar M, et al. Esophageal IgG4 and eosinophilic inflammation correlate in subjects undergoing peanut oral immunotherapy. J Allergy Clin Immunol. 2018 Feb;141, Issue 2, Supplement, Page AB404.

Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol. 1995 Jun;95(6):1179-90.