15 October 2020
EMA/583336/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Palforzia

International non-proprietary name: defatted powder of *Arachis hypogaea* L., semen (peanuts)

Procedure No. EMEA/H/C/004917/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
AAA	Amino acid analysis
AR101	Peanut (Arachis hypogaea) allergens
Ara h x	Where x = 1 to 17, known peanut allergenic proteins
AIT	Allergen Immunotherapy
CHMP	Committee for Medicinal Products for Human Use
CoFAR	Consortium of Food Allergy Research
CSR	Clinical study report
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
EC	European Commission
eCTD	Electronic common technical document
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoE	Eosinophilic esophagitis
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPTN	Golden Peanut and Tree Nuts Company (also known as Golden Peanut Company or GPC)
HPLC	High-performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Initial Dose Escalation
Ig	Immunoglobulin
IHRP	In-house reference preparation
ITT	Intent-to-treat
LC-MS-MS	Liquid chromatography with tandem mass spectrometry

Abbreviation	Definition
LOAEL	Lowest Observed Adverse Effect Level
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MO	Major Objection
NSAID	Nonsteroidal anti-inflammatory drug
OC	Other Concerns
OIT	Oral immunotherapy
OFC	Oral food challenge
OOS	Out of specification
PEESS	Pediatric Eosinophilic Esophagitis Symptom Scores
PDCO	Paediatric Committee
PEI	Paul Ehrlich Institute
PIP	Paediatric investigational plan
RBC	Red Blood Cell
SAWP	Scientific Advice Working Party
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SPT	Skin Prick Test
SmPC	Summary of Product Characteristics
WBC	White Blood Cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aimmune Therapeutics Netherlands submitted on 27 June 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Palforzia, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2017. The applicant was changed during the procedure to Aimmune Therapeutics Ireland Limited.

The applicant applied for the following indication:

Palforzia is indicated as oral immunotherapy (OIT) for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy to reduce the incidence and severity of allergic reactions, including anaphylaxis, after exposure to peanut. Palforzia is also indicated for maintenance of efficacy in peanut-allergic patients who turn 18 years during therapy.

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

Palforzia is not intended for, and does not provide, immediate relief of allergic symptoms.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0114/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance defatted powder of *Arachis hypogaea* L., semen (peanuts) contained in the above medicinal product to be considered as a new active substance in comparison to other products containing *Arachis hypogaea* allergens previously authorised in the European Union as peanut allergens prick test as the applicant claimed that defatted powder of *Arachis*

hypogaea L., semen (peanuts) differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 June 2017	EMEA/H/SA/3579/1/2017/SME/II	Prof. Brigitte Blöchl-Daum, Dr Jan Mueller-Berghaus

The Scientific advice pertained to the strategy for supporting clinical benefit-risk assessment with studies ARC003 and ARC010:

- Adequacy of "ability to tolerate a single, maximum challenge dose of 1000 mg peanut protein with no more than mild symptoms at the Exit DBPCFC" as primary endpoint and associated pre-specified statistical analysis plan for study ARC003
- Acceptability on the overall number of patients included in pivotal trials (ARC003 and ARC010) for defining a benefit-risk
- Support of the population included in pivotal clinical trials for the indication "protection from moderate or severe allergic reactions following accidental exposure"
- Requirements related to need for food challenge prior to treatment with the product

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Mark Ainsworth

The application was received by the EMA on	27 June 2019
The procedure started on	18 July 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	02 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 September 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Palforzia on	15 October 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Peanut allergy is a food-related allergic reaction which tends to begin early in life and progresses to a symptomatic allergy with increasing age. The allergic reaction provoked by peanuts is an immunoglobulin E (IgE)-mediated type I hypersensitivity reaction. It is a potentially serious condition that disproportionately affects children and is associated with severe allergic reactions, including life-threatening anaphylaxis and death.

2.1.2. Epidemiology and risk factors, prevention

In Europe, the prevalence of peanut allergy in children is approximately 1.6% as estimated by food challenges or clinical history[1].

Unlike many other types of food allergies, peanut allergy is usually life-long, with approximately up to 80% of affected individuals remaining peanut-allergic into adulthood[2].

Peanut and tree nut allergies account for the majority of fatal food-induced anaphylaxis [3].

Multiple factors can influence the severity of an allergic reaction, including a history of anaphylaxis to peanut, comorbid conditions (e.g. asthma, cardiovascular disease, mastocytosis), concurrent use of certain medications (e.g. nonselective beta blockers and nonsteroidal anti-inflammatory drugs [NSAIDs]), and exercise. Risk-taking behavior in teenagers and young adults, such as failure to avoid triggers, failure to carry an epinephrine auto-injector, and alcohol use are thought to contribute to severe or fatal anaphylaxis[4]. However, the severity of an allergic reaction after food allergen exposure is not predictable based on any prior reactions or any specific diagnostic marker[5].

Currently, the prevention of a peanut-allergic reaction for individual allergic to peanut is a strict peanut-avoidant diet.

2.1.3. Biologic features, aetiology and pathogenesis

Peanut allergy is classified as an IgE-mediated type I hypersensitivity reaction upon allergen (peanut) contact. On first exposure, the immune system reacts to proteins in the peanuts by producing the antibody IgE which binds to receptors present on mast cells and basophils. Subsequent exposure to peanut leads to an inflammatory response governed by these cells, as the peanut protein causes the IgE/receptor complexes to cross link and active the release of the inflammatory mediators (e.g. histamine) inside them. Histamine and other inflammatory mediators then trigger the symptoms of an allergic reaction.

Allergen-specific immunotherapy (SIT) is an approach, where increasing amounts of an allergen are administered to patients with IgE-mediated (food) allergy to raise the threshold and decrease the severity of allergic responses to the allergenic agents. An oral route of administration of (especially food) allergens like peanut for allergen immunotherapy is called Oral specific ImmunoTherapy (OIT).

Genetic and environmental factors are involved within the pathogenesis of food allergies. An impaired barrier function of the skin is one area of focus.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Clinical features of food allergy may present with a heterogeneous pattern of clinical symptoms. The majority of food induced allergic reactions are IgE-mediated (immediate type, type I hypersensitivity). IgE-mediated allergic reactions may affect every organ system (e.g. skin: flares, urticarial, worsening of atopic dermatitis; gastrointestinal: vomiting, diarrhoea, stomach pain; respiratory tract: dyspnoea,

[1] Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69:992-1007.
[2] 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.
[3] Sampson HA. Food allergy--accurately identifying clinical reactivity. Allergy. 2005;60 Suppl 79:19-24.
[4] Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127(3):587-93.
[5] 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;45(5):859-71.

wheezing, stridor, cough or rhino conjunctivitis; cardiovascular: system hypotension, tachycardia/arrhythmia or cardio-vascular arrest). In addition to objective symptoms, subjective symptoms may be heard to measure, such as dizziness, tingling/burning in mouth and throat, itchiness of skin, eyes or nose, a general discomfort, dysphagia, nausea and others.

The diagnosis of peanut allergy is based on a history of allergic reactions to peanut-containing foods, presence of peanut-specifics-IgE or reaction to peanut allergens on a skin prick test (SPT), a double-blind placebo-controlled food challenge (DBPCFC), or a combination of these.

During the oral food challenge, sequential increasing measured doses of a test allergen are administered until symptoms occur that prevent further dosing, allowing the assessment of both the highest tolerated dose of an allergen and the associated dose-limiting symptoms.

Peanut allergy is the leading cause of severe and life-threatening anaphylactic reactions and death from food allergic reactions[6].

Unlike other childhood allergen reactivity (like milk or egg), peanut allergy does not always resolve with increasing age. Some studies have reported that approximately 20% of children diagnosed with peanut allergy outgrow it [7,8,9]. Another study confirmed peanut allergy by food challenge in patients aged 1 year and reported resolution of peanut allergy in 22% of patients by age 4 years[10]. In patients who become tolerant to peanut, resolution of peanut allergy usually occurs by age 6 years and at a much lower frequency after age 10 years[11].

2.1.5. Management

Currently, no licensed therapeutic options are available within the EU for desensitising individuals with peanut allergy to peanut allergens. The current global standard of care for patients with peanut allergy is peanut avoidance and treatment for allergic reactions due to peanut exposure (adrenaline).

Strict peanut-avoidant diet can be difficult and imposes a significant quality-of-life burden[12]. Despite efforts of strict peanut avoidance, exposure remains a major concern because allergic responses in individuals with peanut allergy may be triggered by minute quantities (< 5 mg) of peanut protein[13] . Strict adherence to an avoidance diet can be complicated by difficulty in interpreting food labels[14] , the presence of undeclared or hidden allergens in commercially prepared foods[15,16], and inattention to or mistrust of food warning labels[17]. Foods prepared outside the home (e.g. at school, day care centres, restaurants, homes of family/friends) present additional potential sources of exposure.

[6] Sicherer SH et al. Advances in diagnosis peanut allergy. J Allergy Clin Immunol Pract. 2013 Jan;1(1):1-13;
[7] 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;121(3):731-6
[8] 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;112(1):183-9.
[9] 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.
[10] Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, 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. 2015:135(5):1257-66.
[11] 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;1(5):528-30.
[12] 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.
[13] 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):610-20.
[14] 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.
[15] 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
[16] 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.
[17] 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.

Food allergen exposures are common, with 55% of individuals with peanut allergy experiencing at least 1 allergic reaction over approximately 5 years[18]. Peanut allergy can negatively affect the health-related quality of life for individuals and their families due to increased stress and anxiety associated with the burden of avoidance, constant vigilance over food choices, and resulting social restrictions and fear of anaphylaxis [19,20,21,22].

Patients and their families are educated to recognise and manage allergy symptoms and on the appropriate use of rescue medications (e.g. epinephrine [adrenaline] auto-injectors) for allergic reactions in the event of exposure. Prompt treatment with intramuscular epinephrine is the first-line treatment for severe systemic allergic reactions[23]. However, not all patients may have ready access to an epinephrine auto-injector. In addition inadequate use, may delay treatment and result in adverse outcomes including hospitalisation and in rare cases, death[24] .

About the product

Palforzia (defatted powder of *Arachis hypogaea* L., semen (peanuts)) has been developed as an OIT to help protect patients with peanut allergy from severe systemic allergic reactions by ultimately modifying the patient's immunologic response to peanut. The active substance defatted powder of *Arachis hypogaea* L., semen (peanuts) is sourced from raw shelled peanuts that are processed into food-grade, light roast, defatted peanut flour. The active substance contains approximately 50% peanut protein (w/w) constituting of a natural mixture of a variety of proteins termed Ara h 1 through Ara h 17. Of the allergenic proteins, Ara h 1, Ara h 2, and Ara h 6 are considered the most clinically important allergens (immunodominant). The remaining components include primarily fats, carbohydrates, minerals, and moisture. The precise mechanism by which OIT desensitises peanut-allergic patients is not fully characterised. Immunologic changes with OIT in clinical trials suggest progression towards a clinical state of desensitisation with with continued peanut OIT. These changes include increases in peanut-specific IgG4, decreases in peanut-specific IgE, decreases in the peanut-specific IgE/IgG4 ratio, increases in peanut-specific regulatory T cell populations, and elimination of peanut-specific Th2A cells.

The applicant applied for the following indication:

Palforzia is indicated as oral immunotherapy (OIT) for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy to reduce the incidence and severity of allergic reactions, including anaphylaxis, after exposure to peanut. Palforzia is also indicated for maintenance of efficacy in peanut-allergic patients who turn 18 years during therapy.

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

Palforzia is not intended for, and does not provide, immediate relief of allergic symptoms.

[18] Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6.
[19] Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Clin Exp Allergy. 2017;47(6):719-39
[20] 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):1297-304.
[21] 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.
[22] 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.
[23] Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy. 2007;62(8):857-71.
[24] Grabenhenrich LB, Dölle S, Ruëff F, Renaudin JM, Scherer K, Pföhler C, et al. Epinephrine in severe allergic reactions: the European anaphylaxis register. J Allergy Clin Immunol Pract. 2018;6(6):1898-906.

The proposed treatment consists of daily administration of gradually increasing doses of peanut protein until a target daily dose does not induce allergic symptoms.

Type of application and aspects on development

The application has been submitted in accordance with Article 8.3 of Directive 2001/83/EC and consists of a complete dossier with administrative, quality, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

For their development the applicant followed in general the relevant CHMP guidelines, including CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006).

The applicant received scientific advices pertaining to quality and clinical aspects of the development from EMA/CHMP (2017) – see Section 1.1.

A PIP was agreed by the Paediatric Committee (PDCO) on 2 October 2015 for the condition 'Treatment of peanut allergy' in children from 1 to less than 18 years of age. A waiver for children below 1 year of age was granted by the PDCO; a study in children from 1 to less than 4 years of age was ongoing (ARC005) at time of submission.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as oral powder in sachets, or capsules for opening; sachets contain 300 mg and capsules for opening contain 0.5 mg, 1 mg, 10 mg, 20 mg or 100 mg of defatted powder of *Arachis hypogaea* L., semen (peanuts) as active substance.

Other ingredients are: partially pregelatinised maize starch (only 0.5 mg, 1 mg, 10 mg and 20 mg strengths), microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

The product is available in either color-coded hydroxypropyl methyl cellulose (HPMC) capsules containing 0.5, 1, 10, 20 or 100 mg of the active substance packaged in PVC: PCTFE/Aluminium blisters (blister strips for initial dose escalation (IDE) and daily dose packs as well as individual blisters for physician in-clinic use) or PET/Aluminium/mLLDPE foil-laminate sachets containing 300 mg of the active substance.

2.2.2. Active Substance

General information

The active substance, defatted powder of *Arachis hypogaea* L., semen (peanuts) is a complex natural product and consequently an International Nonproprietary Name (INN) of the active substance cannot be assigned (INNs are selected in principle only for single, well-defined substances that can be unequivocally characterised by a chemical name or formula). Therefore, a common name of the active substance is used.

The active substance is a partially defatted peanut flour, a light brown to beige fine powder, which represents a natural mixture of allergens (a variety of proteins including proteins termed Ara h 1 through Ara h 17, which have been identified to confer the allergenic properties of peanuts. These allergens vary in their patient sensitivity, abundance, physicochemical properties, and consequently clinical relevance. The most clinically important allergens (Ara h 2, Ara h 6, and to a lesser extent, Ara h 1) are controlled within the active substance specifications.

In addition to routine control of Ara h 1, Ara h 2, and Ara h 6, the presence and consistency of other allergens that also have been demonstrated to bind IgE (Ara h 3, Ara h 7, Ara h 8, Ara h 9, and Ara h 10 through Ara h 17) have been characterised to different extents in lots of the active. Relative to Ara h 1, Ara h 2, and Ara h 6, allergens Ara h 3, Ara h 7, Ara h 8, Ara h 9, and Ara h 10 through Ara h 17 have been reported to have lesser clinical importance as discussed above. All 17 known peanut allergens have demonstrated some prevalence of IgE binding; therefore, pertinent additional information about each Ara h 1 through Ara h 17 is included in the dossier and appropriately discussed.

Solubility, partition coefficient, melting point, pH, and other physicochemical properties are not directly applicable to the active substance due to its heterogenous nature. In addition to the peanut allergens, the active substance contains proteins not known to be allergenic, carbohydrates, fats, and minerals naturally found in peanut, each of which possess different physicochemical properties.

Primary structural information from the World Health Organization and International Union of Immunological Societies (WHO/IUIS) for allergens Ara h 1, Ara h 2, and Ara h 6 which are tested per established specifications are included in Table 1.

Table 1: Structure of Peanut Allergens Ara h 1, Ara h 2, and Ara h 6

Isoallergen	Primary Structure [1] (1-Letter Amino Acid Code)	Amino Acids	Molecular Weight, kDa (Theoretical based on protein sequence)	Comment
Ara h 1.0101	MRGRVSPLML LLGILVLASV SATHAKSSPY QKKTENPCAQ RCLQSCQQEP DDLKQKACES RCTKLEYDPR CVYDPRGHTG TTNQRSPPGE RTRGRQPGDY DDDRRQPRRE EGGRWGPAGP RERERREEDWR QPREDWR RPS HQQPR KIRPE GREGEQEWGT PGSHVREETS RNNPFYFPSR RFSTRYGNQN GRIRVLQRFD QRSR QFQNLQ NHR IVQIEAK PNTLVLPKHA DADNILVIQQ GQATVTVANG NNRKSFNLDE GHALRIPSGF ISYILNRHDN QNLRVAKISM PVNTPGQFED FFPASSRDQS SYLQGFSR NT LEAAFNAEFN EIR R VLLEEN AGGEQEER GQ RRWSTRSSEN NEGVIVKVSK EHVEELTKHA KSVSKKGSEE EGDITNPINL REGEPDLSNN FGK LFEVKPD KKNPQLQDLD MMLTCVEIKE GALMLPHFNS KAMVIVVVNK GTGNLELVAV RKEQQQRGRR EEEEDEDEEE EGSNREVRRY TARLKEGDVF IMPAAHPVAI NASSELHLLG FGINAENNHR IFLAGDKDNV IDQIEKQAK D LAFPGSGEQV EKLIKNQKES HFVSARPQSQ SQSPSSPEKE SPEKEDQEEE NQGGKGPLLS ILKAFN	626	71 kDa (full protein) 69 kDa (mature protein after cleavage of signal sequence)	Signal sequence 1-25 Mature protein 26–626 Glycosylation at position 521 (N-linked (GlcNAc) asparagine)

Isoallergen	Primary Structure [1] (1-Letter Amino Acid Code)	Amino Acids	Molecular Weight, kDa (Theoretical based on protein sequence)	Comment
Ara h 2.0201	MAKLTILVAL ALFLLAAHAS ARQQWELQGD RRCQSQLERA NLRPCEQHLM QKIQRDEDSY GRDPYSPSQD PYSPSQDPDR RDPYSPSPYD RRGAGSSQHQ ERCCNELNEF ENNQRCMCEA LQQIMENQSD RLQGRQQEQQ FKRELRNLPQ QCGLRAPQRC DLEVESGGRD RY	172	20 kDa (full protein) 17 kDa (mature protein after cleavage of signal sequence)	Canonical sequence Signal sequence 1-21 Mature protein 22-172 Disulfide bonds 33↔116 45↔103 104↔152 118↔160
Ara h 2.0101	MAKLTILVAL ALFLLAAHAS ARQQWELQGD RRCQSQLERA NLRPCEQHLM QKIQRDEDSY ERDPYSPSQD PYSPSPYDRR GAGSSQHQER CCNELNEFEN NQRCMCEALQ QIMENQSDRL QGRQQEQQFK RELRNLPQQC GLRAPQRCDL DVESGG	156	18 kDa	Fragment/Isoform
Ara h 6.0101	MAKSTILVAL LALVLVAHAS AMRRERGRQG DSSSCERQVD RVNLKPCEQH IMQRIMGEQE QYDSYDIRST RSSDQQQRCC DELNEMENTQ RCMCEALQQI MENQCDRLQD RQMVQQFKRE LMNLPQQCNF RAPQRCDLDV SGGRC	145	17 kDa (full protein) 15 kDa (mature protein after cleavage of signal sequence)	Signal sequence 1-21 Mature protein 22-145 Disulfide bonds 35↔92 47↔79 80↔128 94↔136 105↔145

[1] WHO/IUIS Allergen Nomenclature Home Page

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance is manufactured commercially from raw shelled peanuts following food GMP at the Golden Peanut Company, USA (GPTN). The active substance manufacturing process has been adequately described.

For manufacture of the active substance, the raw shelled peanuts are first roasted, deskinned and grinded before they are defatted in a hydraulic press and milled. Manufacture of the source material is performed according to food GMP. Active substance release testing activities are performed following pharmaceutical GMP standards. Selection of active substance batches follows a decision flowsheet which is mainly based on alignment of the GPTN certificate of analysis with the active substance specification. The active substance manufacturing process is considered acceptable and in-process controls are adequately set to control the process.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. The selection of starting material is sufficiently justified with literature data which show that these peanuts are commonly consumed in Western countries and that the peanuts are highly comparable in their allergenicity attributes.

No human or animal derived materials are used in the active substance manufacturing process.

Control of critical steps and intermediates

The critical limits and in-process controls for the manufacturing process have been established to ensure the suitability of source material.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process.

Process validation

Full data on process validation of the manufacturing process of the peanut flour from raw shelled peanuts are not provided.

To address the request for an appropriately controlled process, especially with respect to manufacturing steps which might have an impact on the relative potencies of relevant allergens, the applicant includes selection criterion for batches which may be screened for use as the active substance. Considering the nature of the active substance and its intended use, this approach was considered satisfactory.

Manufacturing process development

The active substance used in clinical batches was manufactured at the same manufacturer as those intended for commercial use.

Only minor changes to the source material manufacturing process at GPTN have been implemented over the course of clinical development of Palforzia, in order to improve the protection of the active substance during the manufacturing process and/or to increase plant capacity. These changes have been sufficiently justified.

Characterisation

In line with the requirements of the Ph. Eur. monograph 1063 "Allergen Products", it was demonstrated by combination of electrophoretic and immune methods that the relevant allergens Ara h 1, 2 and 6 are present in the active substance and finished product batches. The active substance is characterised by general protein profiling (SDS-PAGE, LC-MS-MS) and allergen characterisation techniques (immunoblotting, ELISA) including data on extractability studies. Potential impurities like pesticides, elemental impurities and aflatoxins relate to the production and storage of peanuts and are appropriately controlled.

Specification

The active substance specifications include appropriate tests and acceptance criteria for this type of product: appearance (visual), identification (HPLC), protein integrity (HPLC), relative potency (ELISA), total allergenic activity (ELISA), assay (total protein) (combustion), loss on drying (gravimetric), particle size distribution (laser diffraction), microbiological limits (Ph. Eur.), specified organisms (Ph. Eur.), aflatoxin (UPLC) and elemental impurities (ICP-MS).

The active substance release testing follows pharmaceutical GMP and includes controls for aflatoxin and pesticide content which have been found to be acceptable.

The tests and assays as indicated in the monograph "Allergen Products" (01/2019:1063) and section "5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use" (01/2014:50104) of the Ph. Eur. including assays for total allergenic activity, relevant allergens, protein profile and protein content are performed for release testing of the active substance. Moreover, testing for heavy metals, pesticides and loss on drying which are tests required for herbal drugs according to the monograph "Herbal Drugs" (01/2017:1433) are included.

Apart from the tests and assays listed in the monographs 1063, 1433 and section 50104 of the Ph. Eur., the following tests are included: appearance, protein integrity via HPLC as well as particle size distribution. Tests and acceptance criteria established are generally considered adequate.

Potency testing of the active substance, the finished product, as well as the in-house reference preparation (IHRP) at release and for demonstration of stability fulfils the requirements of the Ph. Eur. monograph 1063 "Allergen Products" in combination with the EMA Guideline on allergen products: production and quality issues (EMEA/CHMP/BWP/304831/2007).

Since the protein content of a respective active substance batch may vary within the established acceptance criteria, relative potencies are narrowed as such that the variability of the protein content per mg active substance is incorporated into the respective acceptance criteria to comply with Ph. Eur. 1063.

The selection of elemental impurities to test in the active substance and corresponding limits were established in conformance with ICH Q3D, Elemental Impurities. However, herbal products or allergen extracts are out of the scope of this guideline. Thus, the limit for mercury (Hg) will be adapted to comply with Ph. Eur. 1433 prior to commercial testing.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. It is adequately demonstrated that the analytical procedures are suitable for their respective purposes. The applicant committed to performing additional validation studies to further support the relative potency ELISA method across the proposed specification according to ICH guidance Q2(R1) and to submit these data by Q1/2021.

Batch analysis

Batch analysis data for commercial scale batches are provided, of these, several batches were tested for relative potencies. All results comply with the specifications and confirm consistency of the manufacturing process.

Reference materials

An active substance batch is used as internal reference standard since official standards are not available. The same IHRP is used for the active substance and finished product testing. A qualified secondary reference standard will be used in commercial routine testing of the active substance and finished product. The applicant commits to include testing of total allergenic activity in the annual stability program (REC3). The applicant commitment to develop acceptance criteria for the human serum pool once more data will have been collected is accepted (REC6).

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life of 24 months in the proposed container.

Real time, real condition stability data on three commercial scale batches of active substance from the commercial manufacturing process stored at 2 to 8°C RH in the representative container for 36 months and for up to 36 months under accelerated conditions at or 25°C / 60% according to the ICH guidelines were provided.

Results on stress conditions (treatment by acid, base, peroxide, heat, light) were also provided on one batch. Changes in relative potency and protein integrity were observed in the active substance stressed by acid, base, or peroxide treatment. These 3 stress conditions (treatment by acid, base, and peroxide) are extreme, thus changes in the product are not unexpected under regular storage

conditions. The forced degradation studies show that the 2 main stability indicating methods (the relative potency ELISA and protein integrity by HPLC) are capable of detecting degradation of the active substance. The product was stable under the heat and light (photostability) stress conditions.

The studies are performed in line with ICH Q1A and ICH Q5C as well as EMA-guideline EMEA/CHMP/BWP/304831/2007. Based on the commitment provided by the applicant to demonstrate correlation between total allergenic activity and relative potencies of relevant allergens and to include testing of total allergenic activity in on-going and annual stability studies, the claimed shelf life of 24 months can be granted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is sachets or hard hydroxypropylmethyl cellulose (HPMC) capsules for opening containing peanut protein as defatted powder of *Arachis hypogaea* L., semen (peanuts), in a dry-blend mixture of the active substance with excipients and is intended for oral immunotherapy. In order to supply adequate doses for a complex up-dosing scheme, Palforzia is presented as 0.5 mg, 1 mg, 10 mg, 20 mg, 100 mg and 300 mg peanut protein individual dosage strengths. In order to facilitate the dosing scheme (SmPC 4.2), the finished product is packaged in combinations of individual dosage strengths in several packaging configurations. The finished product packaging configuration includes an initial dose escalation (IDE) blister, individual blister (or sachet) cartons at each dose level for physician in-clinic up-dosing, a daily dose pack at each dose level for in-home up-dosing, and a carton of sachets for maintenance.

For Palforzia, the biological activity correlates with the protein content. Therefore, indicating the strength in mass of peanut protein is in line with the requirements of the EMA allergen guideline. This point is discussed further in the report.

In addition to the active substance, the finished product in capsules (0.5 mg, 1 mg, 10 mg and 20 mg is formulated with the following excipients: partially pregelatinised maize starch (NF/Ph Eur; diluent), microcrystalline cellulose (NF/Ph Eur; diluent), colloidal silicon dioxide (NF/Ph Eur; glidant), magnesium stearate (NF/Ph Eur; lubricant).

In addition to the active substance, the finished product in capsules (100mg) and sachets is formulated with the following excipients: microcrystalline cellulose (NF/Ph Eur; diluent), colloidal silicon dioxide (NF/Ph Eur; glidant), magnesium stearate (NF/Ph Eur; lubricant).

A dry powder formulation was developed based on the proposed oral route of administration and the need for the product to be mixed evenly with semi-solid food. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Binary compatibility studies were performed at 40°C / 75% RH over 2 months to assess the compatibility of each excipient independently with the active substance, giving satisfactory results.

The general process for manufacture of Palforzia has not changed from phase 2 to phase 3 clinical trials and from phase 3 to commercial production. In each transition, the powder blend batch size increased to accommodate the clinical or commercial demand. The equipment used to accommodate this increase in batch size is of the same design and operating principle.

Data provided on process development are appropriate to support the manufacturing process, process parameters as well as in-process controls and controls of critical steps.

Changes in equipment, manufacturing scale and production area were introduced between manufacture of clinical phase 3 and commercial batches. Comparability exercise was performed and demonstrated comparability of clinical and commercial batches.

The product is available in either colour-coded hydroxypropyl methyl cellulose (HPMC) capsules containing 0.5, 1, 10, 20 or 100 mg of the active substance packaged in PVC:PCTFE/Aluminium blisters (blister strips for initial dose escalation (IDE) and daily dose packs) or PET/Aluminium/mLLDPE foil-laminate sachets containing 300 mg of the active substance. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the finished product involves powder blending, bulk finished product encapsulation (0.5, 1, 10, 20, and 100 mg strengths) or sachet filling (300 mg strength only), and packaging (primary and secondary), as applicable.

Information on the storage containers used and potential holding times established for intermediates during manufacture of the finished product are included. Blend bulk and encapsulated bulk hold times are sufficiently justified by suitable stability data.

Relevant process parameters are included with set points or ranges justified by pharmaceutical development data included in the dossier. Based on the risks identified during development, critical steps have been identified and adequate controls of critical steps to monitor the critical material attributes and critical process parameters are included.

Prospective process validation was performed. The justification provided for the approach is comprehensible and the set-up is considered suitable to demonstrate adequate validity of the finished product manufacturing process for all strengths. Three consecutively manufactured batches of the 0.5, 20, 100 or 300 mg strength were included in validation of each process step, i.e. blending and encapsulation or sachet filling in line with EMA-guideline "Guideline on process validation for finished products - information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1). Batches were manufactured at the target batch size (commercial scale). The blistering process was validated separately. Results of process parameters and of extended testing as well as release data are included for all PPQ batches. All results met the pre-defined acceptance criteria. Therefore, the conclusion of the applicant that the process is considered adequately validated and suitable for manufacture of the finished product can be followed. Results of shipping validation studies will be available by the second quarter of 2020.

Product specification

The finished product specifications include typical tests for this type of the finished product: appearance (visual), identification (HPLC), protein integrity (HPLC), relative potency (ELISA), total allergenic activity (ELISA), assay (total protein) (combustion), loss on drying (gravimetric), deliverable mass (gravimetric),content uniformity (Ph. Eur.), microbiological limits (Ph. Eur.), specified organisms (Ph. Eur.) and aflatoxin (UPLC).

Since potency is reported based on the protein content at the active substance level, which is considered acceptable, and since the strength of the product is adjusted based on the protein content, it is assured that each mg of peanut protein has a controlled potency.

All presentations of AR101 finished product capsules are packaged into thermoformed blister strips with foil-backing (pharmaceutical-grade PCTFE (polychlortrifluorethylen) film lamination). Push-through (for IDE and daily dose packs) lidding materials are used. Sachets are made from a 3 layer foil-laminate film. The foil-laminate is composed of polyethylene terephthalate (PET)/aluminium

foil/polyethylene (mPE). Paperboard cartons are used as secondary packaging. The information provided on the container closure system is sufficient. All plastic materials used as container closure comply with the requirements of Ph. Eur. 3.2.2.

The applicant commits to evaluate the content uniformity data on a sufficient number of 1 mg drug product lots manufactured at commercial scale for setting the acceptance criteria according to Ph Eur 2.9.40 and also to include 0.5 mg lots for evaluation (REC4).

Test and acceptance criteria implemented for release testing of the finished product comply with (or are stricter than) the requirements of the Ph. Eur. monograph 1063 "Allergen Products", 1433 "Herbal drugs" and 1165 "Powder, oral" and corresponding section 2.9.40 and 5.1.4 of the Ph. Eur. as well as with ICH guideline Q6A and Q6B.A commitment is provided to reassess the specifications once batch analysis data from additional commercial batches will be available (REC2).

According to the Ph. Eur. monograph 1063 "Allergen Products", a validated test measuring the potency should be included in testing of allergen products intended for therapeutic use. This test should be performed as late as possible in the manufacturing process. Total allergenic activity will be included for release and stability testing of the finished product initially. To reduce the risk of doses differing in allergenic content, after introduction of a new dose in the clinic, each patient receives subsequent doses for application at home from the same finished product batch which was used for up-dosing in the clinic until the maintenance dose of 300 mg is reached. If a combination of different strengths is applied, each strength which is taken at home will be derived from the same batch of a respective strength which was used for up-dosing in the clinic.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine was performed in accordance with the document "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020. The risk of nitrosamine or its precursors being present in the finished product is rated as being extremely low.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Reference materials

The same reference standard, made from a lot of the active substance, is used for both active substance and finished product assays.

Batch analysis

Batch analysis data on commercial scale batches of the finished product were provided. The data provided are generally considered sufficient to demonstrate adequate batch-to-batch consistency of the different finished product strength. The results confirm consistency of the manufacturing process.

Stability of the product

Real time/real condition stability data of pilot scale batches of finished product covering all strengths for up to 36 months stored at 2 to 8°C and for up to 36 months at 25 ºC / 60% RH according to the ICH guidelines were provided. Taking into account that the finished product is a dry powder blend, the

bracketing approach described by the applicant is considered acceptable. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, commercial scale batches covering all strengths by a matrix design stored at 25°C /60% RH or 30°C / 65% RH over 12 months and at 40°C / 75% over 6 months were provided. These studies are still ongoing. Moreover, supportive stability data provided for phase 3 clinical batches stored over 36 months and data provided from degradation studies were included. Thus, since comparability between clinical phase 3 and commercial scale batches was sufficiently demonstrated, a shelf life for the finished product of 24 months can be granted. All results complied with the acceptance criteria in current specifications.

Total allergenic activity will be included in the on-going and new stability studies until a correlation between relative potency/-ies of single allergens and total allergenic activity have been demonstrated (REC3).

Data collected from forced degradation studies indicate that Palforzia was stable under heat and light stressed conditions. The analytical data from heat, light, acid, base, and oxidation stress conditions support the stability indicating nature of the methods.

Data collected from a temperature cycling study indicate that Palforzia was stable even after multiple temperature cycling between -20°C and 40°C. The two temperatures that the finished product was cycled between, represent the possible extreme conditions that finished product might be exposed to during shipping or during usage by a patient.

Based on available stability data, the shelf-life of 2 years and storage conditions: the product should not be stored above 25°C, as stated in the SmPC, are acceptable.

Adventitious agents

All materials used in the manufacture of the finished product are either plant-based or inorganic materials. None of the materials in the finished product contain products of animal origin or animal-derived products. The lubricant (stearate) used in the manufacture of the sachet foil laminate material, which is in direct contact with the finished product, is derived from the tallow of ovine, bovine, and caprine sources. However, given the processing conditions used during the manufacturing of the tallow derivatives, there is no concern regarding these materials with respect to either virus or TSE safety.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance used in production of Palforzia is a partially defatted lightly roasted peanut flour. It is manufactured from semen of *Arachis hypogaea* by the Golden Peanut Company, USA according to food GMP. Active substance release testing follows pharmaceutical GMP. The finished product is a dry-blend mixture of the active substance with Ph. Eur. grade excipients and is intended for oral immunotherapy presented in capsules for opening containing 0.5, 1, 10, 20, or 100 mg peanut protein, or in sachets containing 300 mg peanut protein.

The active substance is manufactured according to standards for conventional food use. While some requirements of the EU-GMP guideline Annex 2 on Manufacture of Biological active substances and Medicinal Products for Human Use are not fully covered, adequate improvements were introduced to

assure that batches which were not produced within narrowed justified ranges will not be used for manufacture of Palforzia.

Potency testing of the active substance, the finished product as well as the in-house reference preparation (IHRP) at release and for demonstration of stability is performed in line with the requirements of the Ph. Eur. monograph 1063 "Allergen Products" in combination with the EMA Guideline on allergen products: production and quality issues. The applicant also included, testing of total allergenic activity for finished product release at least until results from validation studies in line with ICH Q2 will be provided, which is expected in Q1/2021.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which will be addressed as Recommendations for future quality development post marketing.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Proposed list of recommendations:

Area	Number	Description	Classification	Due date
Quality	1	The applicant commits to validate the relative potency assays for single allergens in line with ICH Q2 and provide results in Q1/2021	REC	Q1/2021
Quality	2	The applicant commits to assess commercial specification acceptance criteria for the individual allergen ELISA and the TAA/individual allergen ELISA correlation studies.	REC	End of 2022
Quality	3	The applicant commits to additionally include TAA testing for on-going commercial scale stability studies.	REC	At appropriate time-points
Quality	4	The applicant commits to collect content uniformity data of 1 mg and 0.5 mg and agrees to evaluate the content uniformity data for setting the acceptance criteria according to Ph Eur 2.9.40.	REC	December 2022
Quality	5	The applicant commits that once validation is complete, the method for determination of	REC	On completion

		aflatoxin content at a secondary CTL will be implemented.		
Quality	6	The applicant commits that acceptance criteria for Ara h 6 will be developed for the human serum pool once more data will have been collected.	REC	On availability

2.3. Non-clinical aspects

2.3.1. Introduction

Palforzia's active substance (defatted powder of *Arachis hypogaea* L., semen (peanuts)) is food-grade, defatted, roasted peanut flour that contains approximately 50% peanut protein (w/w). Peanut flour (containing fats, carbohydrates, fiber, vitamins, and minerals as well as protein) is a standard foodstuff, consumed in the diet at levels higher than the intended clinical use.

Due to the nature of the active substance, a food-derived product, non-clinical studies with Palforzia have not been performed. This was discussed and agreed with the PDCO during the development program of Palforzia.

The non-clinical data package submitted by the applicant consists of justifications for not performing *in vitro*/ *in vivo* studies and literature references.

2.3.2. Pharmacology

Primary pharmacodynamics

In vitro studies

Peanuts contain multiple Ara h proteins, including Ara h 1 through Ara h 9 that provide specific functions within the peanut seed and are thought to have allergenic properties. Based on *in vitro* serology and histamine release assays, Ara h 1, Ara h 2, and Ara h 6 are believed to be the most common and potent peanut allergens, with Ara h 2 and Ara h 6 contributing the majority of the allergenic activity of crude peanut extract (Zhuang, 2013[25]; Porterfield, 2009[26]). Therefore, the Palforzia active substance, which contains all peanut allergens, was tested for its relative (to a reference standard) potency of Ara h 1, Ara h 2, and Ara h 6 using an enzyme-linked immunosorbent assay. As determined by reversed-phase high performance liquid chromatography, the expression of these proteins was consistent, both individually and relative to each other, across numerous lots of Palforzia active substance.

[25] Zhuang Y, Dreskin SC. Redefining the major peanut allergens. Immunol Res. 2013;55(0):125-134.
[26] Porterfield HS, Murray KS, Schlichting DG, et al. Effector activity of peanut allergens: a critical role for Ara h 2, Ara h 6, and their variants. Clin Exp Allergy. 2009;39(7):1099-1108.

In vivo studies

The applicant presented data from a literature search encompassing non-clinical pharmacology data generated in a mouse model of peanut allergy[27,28,29,30].

In these studies, the principal model for induction of peanut allergy in mice was exposure by oral gavage to peanut proteins in the form of ground roasted peanuts (Kulis, 2012)[27], peanut butter (Sun, 2007), or purified peanut proteins in combination with cholera toxin (Mondoulet, 2012)[29]. After 3 to 6 weekly exposures, the mice were challenged to demonstrate an allergic response. Several *in vivo* respectively para-clinical parameters for desensitisation were introduced (e.g. change in body temperature, symptom scores, vascular permeability, mast cell mediator release, detection of allergen specific antibodies, cytokine release, or the analysis of various immune cells in detail).

In the study by Kulis (2012)[27], the authors concluded that Ara h 2 and Ara h 6 were responsible for the majority of effector activity in this peanut allergy mouse model and immunotherapy with Ara h 2/Ara h 6 can effectively desensitise the mice to a degree equivalent to crude whole peanut extract containing all major allergens.

In the study by Sun (2007)[28], the authors concluded that both antigen-specific IgE and mast cells were necessary and sufficient to induce anaphylaxis in peanut protein-allergic mice.

In the study by Mondoulet (2012)[29], epicutaneous immunotherapy (EPIT) reduced the Th2 immunological response, esophageal eosinophilia, mRNA expression of Th2 in tissue and intestinal villus atrophy. Additionally, EPIT increased specific IgG2a and mRNA expression of Foxp3 in the esophageal mucosa.

In the study by Wagenaar (2019)[30], the mice showed a reduction in the drop in body temperature (i.e., symptoms of anaphylactic shock) and increase in IgG2a levels in response to peanut extract challenges. Similarly, no anaphylaxis was seen in BALB/c mice and a clear effect of OIT was observed on Th2-linked antibody and cytokine responses. Specific antibody responses showed similar patterns in both strains for IgA and IgG1.

The applicant noted that there are inherent limitations of the animal models such as induction of the food allergy requiring co-administration with cholera toxin, and intraperitoneal/intradermal rather than oral challenge. Effector responses and anaphylaxis intensity may vary depending on whether the challenge is oral or systemic (such as intraperitoneal) (Joost, 2011)[31].

Secondary pharmacodynamics, safety pharmacology, pharmacodynamics drug interaction studies

The applicant stated that Palforzia's substance contains components of partially defatted, roasted peanut flour which are standard human dietary constituents consumed in the diet at levels higher than the intended clinical use. Therefore, secondary pharmacodynamics investigations, safety pharmacology and pharmacodynamics drug interaction studies have not been performed.

[27] Kulis M, Chen X, Lew J, et al. The 2S albumin allergens of Arachis hypogaea, Ara h 2 and Ara h 6 are the major elicitors of anaphylaxis and can effectively desensitize peanut-allergic mice. Clin Exp Allergy. 2012;42(2):326-336.

[28] Sun J, Arias K, Alvarez D, et al. Impact of CD40 ligand, B cells, and mast cells in peanut-induced anaphylactic responses. J Immunol. 2007;179(10):6696-6703.

[29] Mondoulet L, Dioszeghy V, Larcher T, et al. Epicutaneous immunotherapy (EPIT) blocks the allergic esophago-gastro-enteropathy induced by sustained oral exposure to peanuts in sensitized mice. PLoS One. 2012;7(2):e31967.

[30] Wagenaar L, Bol-Schoenmakers MW, Giustarini G, et al. Mouse strain differences in response to oral immunotherapy for peanut allergy. Immunity, Inflammation and Disease. 2019;7:41-51

[31] Joost S, Maarten P, Geert H, et al. The individual role of peanut proteins Ara h1, 2, 3 and 6 in peanut allergy. Clin Translational Allergy. 2011:1(Suppl 1);O36.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism and excretion of the components of the peanut flour active substance will follow normal human dietary component PK/metabolic pathways, as expected from a foodstuff containing proteins, fats, carbohydrates, fibre, vitamins and minerals. After oral administration, the proteins are hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract. Therefore, no pharmacokinetics studies have been conducted.

2.3.4. Toxicology

Preclinical toxicity studies, including juvenile toxicity studies, with Palforzia have not been performed as the safety of peanut flour as a common food and food additive is assured.

However, in contrast to peanut flour as foodstuff, some excipients are contained in the Palforzia formulation. The finished product is formulated with starch 1500 (partially pregelatinised maize starch), microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate as excipients. All the excipients used are widely used and of Ph Eur compendial grade and considered to be safe and appropriate for use in pharmaceutical products for both children and adults. There are no novel excipients in the Palforzia formulations, and no safety issues presented by the excipients.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance (derived from food), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Palforzia is not expected to pose any risk to the environment. Dedicated ERA studies are not considered necessary and the submitted expert statement is acceptable.

2.3.6. Discussion on non-clinical aspects

The *in vivo* pharmacology data in a mouse model of peanut allergy, presented from the literature, provided information on involved immunological players or pathophysiological changes within peanut allergy and immunological and clinical effects of desensitisation. Nevertheless, the value of *in vivo* (mouse) models of human food allergy is still limited. Therefore, robust conclusions on the pharmacodynamic effects of peanut OIT in human cannot easily be transferred from the mouse model.

No pharmacokinetics studies have been performed. The applicant has briefly justified the absence of data, which is agreed due to the nature of the product being mainly proteins which are rapidly metabolised to peptides and amino acids not detectable in body fluids.

It is agreed that non-clinical safety studies are not regarded necessary as peanuts are commonly used foods and food additives. Peanut flour is an ingredient in many food products, regarding the product in question Palforzia it is dosed in relatively small quantities (up to 300 mg daily), and is administered via the same route as orally ingested, peanut-containing products. It is also acknowledged that the excipients are well-known and not suspected to harbour any toxic properties. Impurities with known toxic or carcinogenic effects as aflatoxins, heavy metals and pesticides are controlled by the specifications, which are aligned with European and U.S. requirements for foodstuff.

Furthermore, it is agreed that a specific juvenile animal study is not considered needed in view of existing clinical experience in children with peanut OIT as well as the limited value of mouse models of human food allergy.

Finally, clinical studies performed with Palforzia did not identify any unexpected safety signal and the adverse event profile complies with known side effects of OIT.

2.3.7. Conclusion on the non-clinical aspects

The absence of a non-clinical development for Palforzia is acceptable in view of the nature of the active substance and the use of well-known excipients with no potential for toxicity.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program was designed to demonstrate the efficacy and safety of Palforzia in children and adolescents with a confirmed diagnosis of peanut allergy in reducing the incidence and severity of allergic reactions after exposure to peanut, in conjunction with a peanut-avoidant diet.

Two phase II studies (ARC001, ARC002) and 7 phase III studies (ARC003, ARC004, ARC005, ARC007, ARC008, ARC010, ARC011) were conducted. The main pivotal efficacy and safety studies are ARC003 (Europe and North America) and ARC010 (Europe only) (Table 2).

Classical phase I studies in healthy individuals have not been conducted and are not considered appropriate for allergen products, since they do not provide helpful information in terms of safety and tolerability (CHMP/EWP/18504/2006).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 **Tabular overview of clinical studies**

Study Identifier [1]	**Status, Location, No. of Subjects [2]**	**Study Design**	**Ages**	**Primary Outcome Measure**
Palforzia studies that support the MAA				
ARC001 NCT01987817	Completed US Enrolled: 56 Completed: 49	Phase 2, randomised, double-blind, placebo-controlled Maintenance: 2 weeks	4-26 years	Efficacy: Proportion of subjects who achieve desensitisation (tolerate at least 300 mg [443 mg cumulative] peanut protein with no more than mild symptoms at the exit DBPCFC)

ARC002 NCT02198664	Completed US Enrolled: 47 Completed: 23	Phase 2 open-label follow-on for ARC001 Maintenance: ~3-6 months	Per prior study	Safety: Incidence of treatment-related adverse events and dosing symptoms occurring with peanut OIT over a treatment period of at least 18 months
ARC003 NCT02635776 2015-004257-41	Completed CA, Europe, US Enrolled: 555 Completed: 442	Phase 3, randomised, double-blind, placebo-controlled Maintenance: ~6 months	4-55 years	Efficacy: Proportion of subjects aged 4-17 years who achieve desensitisation (tolerate a single dose of at least 1000 mg [2043 mg cumulative, Europe] peanut protein or at least 600 mg [1043 mg cumulative, North America] peanut protein with no more than mild symptoms at the exit DBPCFC)
ARC004 NCT02993107 2016-004941-94	Ongoing CA, Europe, US Group 2, cohort 1 Enrolled: 117 Completed: 107	Phase 3 open-label follow-on for ARC003 Maintenance: ~6 months	Per prior study	Safety: Frequency of treatment-related adverse events and serious adverse events during the overall study period
ARC007 NCT03126227	Completed CA, US Enrolled: 506 Completed: 418	Phase 3, randomised, double-blind, placebo-controlled Maintenance: none	4-17 years	Safety: Frequency of treatment-emergent adverse events including serious adverse events during the overall study period
ARC008 NCT03292484 2017-001334-26	Ongoing CA, Europe, US Enrolled: 633 Completed: 0	Open-label follow-on for designated current and future Palforzia Maintenance: varies studies	Per prior study	Safety: Frequency of treatment-emergent adverse events during the overall study period

ARC010 NCT03201003 2016-005004-26	Completed Europe Enrolled: 175 Completed: 146	Phase 3, randomised, double-blind, placebo-controlled Maintenance: ~3 months	4-17 years	Efficacy: Proportion of subjects who achieve desensitisation (tolerate a single dose of at least 1000 mg [2043 mg cumulative] peanut protein with no more than mild symptoms at the exit DBPCFC)
ARC011 NCT03337542	Ongoing CA, US Enrolled: 243 Completed: 167	Phase 3 open-label maintenance for ARC007 (Palforzia-treated) Maintenance: ~6 months	Per prior study	Safety: Frequency of treatment-emergent adverse events including serious adverse events during the overall study period
Additional Palforzia studies				
ARC005 NCT03736447 2018-001749-15	Ongoing Europe, CA, US Enrolled [3]: 0 Completed: 0 Study start-up activities ongoing	Phase 3, randomised, double-blind, placebo-controlled Maintenance: ~3-6 months	1 to < 4 years	Efficacy: Single highest tolerated dose of at least 600 mg peanut protein with no more than mild symptoms in the exit DBPCFC

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

[2] Data cut-off date 15 Dec 2018 for ongoing studies. Completed indicates a clinical study report is available.

[3] First subject was randomised in December 2018.

CA, Canada; DBPCFC, double-blind, placebo-controlled food challenge; MAA, marketing authorization application; OIT, oral immunotherapy; US, United States.

2.4.2. Pharmacokinetics

Palforzia is a non-derivated/purified food-derived product which is given orally in small amounts via the same route of administration as normal consumption of food (i.e. peanuts). Components of peanut flour are in general standard human dietary constituents.

Palforzia's active substance (defatted powder of *Arachis hypogaea* L., semen (peanuts)) is sourced from raw shelled peanuts that are processed into food-grade, light roast, defatted peanut flour. The active substance contains approximately 50% peanut protein (w/w) (proteins Ara h 1 to Ara h 17). The remaining components include primarily fats, carbohydrates, minerals, and moisture. Therefore, the active ingredients of Palforzia contain naturally occurring allergenic peanut proteins, which are underlying the physiologic digestion. After oral administration, the proteins are hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract.

In accordance with the CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006), no clinical studies investigating the pharmacokinetic profile and metabolism of Palforzia have been conducted.

2.4.3. Pharmacodynamics

Mechanism of action

In general, peanut allergy may be classified as an IgE-mediated type I hypersensitivity reaction upon allergen (peanut) contact. In such reactions, peanut-specific IgE antibodies are thought to bind to high-affinity receptors on mast cells and basophils. Allergen- SIT is an approach, where increasing amounts of an allergen are administered to patients with IgE-mediated (food) allergy to raise the threshold and decrease the severity of allergic responses to the allergenic agents. An oral route of administration of (especially food) allergens like peanut for allergen immunotherapy is called OIT.

The mechanism by which OIT desensitises peanut-allergic patients has not been definitely characterised. However, described immunologic changes in line with a "successful" desensitization upon OIT (or SIT), include increases in allergen-specific IgG4, decreases in allergen-specific IgE, decreases in the allergen-specific IgE/IgG4 ratio, increases in allergen-specific regulatory T cell populations, and others.

The described general mode of action including presented data on correspondent trials within the applicant's development program goes in line with current hypothesis of specific immunomodulatory responses in SIT respectively OIT.

Primary and Secondary pharmacology

In accordance with the CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006), no formal pharmacodynamics studies were conducted with Palforzia. Data on the immunologic changes (i.e. peanut-specific IgE and IgG4) were measured in efficacy/safety clinical trials performed with Palforzia.

Thus, changes of immunoglobulins and changes of wheal-size following SPT are presented in the efficacy part of the dossier (please refer to ancillary efficacy results for assessment).

2.4.4. Discussion on clinical pharmacology

Palforzia contain naturally occurring allergenic peanut proteins (proteins Ara h 1 to Ara h 17). After oral administration, the proteins are hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract.

Peanut allergy may be classified as an IgE-mediated type I hypersensitivity reaction upon peanut contact. The precise mechanism of action of desensitisation is not fully understood. However, described immunologic changes in line with a "successful" desensitization upon OIT (or SIT), include increases in allergen-specific IgG4, decreases in allergen-specific IgE, decreases in the allergen-specific IgE/IgG4 ratio, increases in allergen-specific regulatory T cell populations, and others. The described general mode of action including presented data on correspondent trials within the applicant's development program go in line with current hypothesis of specific immunomodulatory responses in SIT respectively OIT.

Pharmacokinetic studies are not possible for products of specific immunotherapy. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the

nature of the product (CHMP/EWP/18504/2006). In addition, systemic levels of Palforzia are not relevant for the process of OIT, which depends in part on oral delivery and presentation to the immune system associated with draining gut-associated lymphoid tissue.

Formal pharmacodynamic studies are also not possible for allergen products. However, to show the effect of specific immunotherapy on the immune system immunological changes (e.g. changes in allergen-specific IgG levels, T-cell responses, and/or cytokine production) and/or modifications of the endorgan specific response (e.g. provocation tests) should be measured (CHMP/EWP/18504/2006). Therefore, changes of immunoglobulin levels and changes of wheal-size following SPT are presented in the efficacy part of the dossier.

Therefore, for the clinical development of Palforzia, no formal pharmacokinetics and pharmacodynamics studies have been conducted. This is in line with the CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006) and agreed by CHMP.

2.4.5. Conclusion on clinical pharmacology

Due to the nature of the active substance and the intended use of Palforzia, the absence of pharmacokinetics and pharmacodynamics studies is acceptable and in line with the CHMP guideline (CHMP/EWP/18504/2006). The effect of specific immunotherapy on the immune system immunological changes have been measured in the clinical efficacy/safety studies.

2.5. Clinical efficacy

Palforzia clinical development program in children, adolescents, and adults with peanut allergy included

- 2 phase 2 studies (ARC001, ARC002) and
- 7 phase 3 studies (ARC003, ARC004, ARC005, ARC007, ARC008, ARC010, ARC011).

At time of the marketing authorisation application, study conduct was complete for the phase 2 studies ARC001 and ARC002; 2 pivotal phase 3 efficacy and safety studies, ARC003 (Europe and North America) and ARC010 (Europe only); and the phase 3 safety study ARC007 (North America only). During the evaluation, ARC004 study was finalised (14 Feb 2020) and the final study report submitted for assessment.

2.5.1. Dose response studies

Correspondent to the concept of specific immunotherapy, increasing amounts of peanut allergen were administered to peanut allergic patients in order to induce and maintain a state of so-called desensitisation to peanut protein. Consequently, the patient is thought to tolerate a higher amount of peanut protein without severe symptoms and potentially life-threatening systemic allergic reactions resulting from an accidental exposure to nontrivial amounts of peanut.

Selection and timing of each dose of peanut protein (Palforzia) was based on literature data, including the work of the Consortium of Food Allergy Research (CoFAR). Stepwise increasing amounts were applied during initial-day dose escalation, up-dosing, and maintenance.

Results from phase 2 studies ARC001 and ARC002 demonstrated that a clinically desensitisation was reached after initial dose escalation, up-dosing, and maintenance dosing with Palforzia at 300 mg/day. Desensitisation to at least 300 mg peanut protein with daily Palforzia treatment is expected by the

applicant to provide a clinically meaningful level of protection against most accidental exposures to peanut. The applicant declared that although the level of exposure to peanut protein in most accidental exposures is unknown, most clinically relevant accidental exposures are believed to occur at low levels. This expectation is based – among others - on data of *the MIRABEL* survey, a real-world observational study conducted in France, Belgium, and Luxembourg in 785 peanut-allergic patients. Here the real-life eliciting dose for allergic reactions due to accidental exposure was estimated to be a median of 125 mg peanut protein (range, 34-177 mg)[32].

Based on ARC001 and ARC002 studies, the dosing regimen used in the phase 2 studies was used in the pivotal phase 3 studies ARC003 and ARC010.

In general, this approach (based on literature plus experiences in food allergen OIT studies) is accepted. However, it was acknowledged that a "classical dose-finding" for Palforzia has not been performed. During the evaluation, CHMP questioned if differences in the timing schedule including a more prolonged and slower up-dosing or a prolonged maintenance period, including a lower maintenance dose (< 300 mg) might have had the same clinical effect (but probably less side effects). The applicant explained that tthe choice of maintenance dose was a balance between achieving clinically relevant efficacy and not increasing the dose to levels resulting in an inacceptable frequency of adverse events. It was argued that in opposite to lower doses of maintenance (which although was not been presented), "Palforzia phase 2 data indicated that the gain in efficacy with a high maintenance does (e.g. 1000mg or higher) would not be clinically justified. Lower doses of maintenance were not discussed. Instead it was claimed that Palforzia phase 2 data and published literature utilising 300mg maintenance (equivalent protein content of approximately 1 peanut kernel), supported progressing to the pivotal phase 3 studies with a maintenance dose of 300 mg/day.

The applicant also made reference to a placebo-controlled peanut OIT study[33] in which slower up-dosing and lower maintenance doses were used. This small study (62 subjects) suggest that slower up-dosing may lead to fewer adverse events leading to study discontinuation, while eventually reaching desensitisation. However, the primary endpoint of this study was tolerating at least 300 mg peanut protein, not the 1000 mg level (as a single dose) that was required to support the Palforzia studies. The applicant concluded that these data were interesting but do not provide robust evidence of efficacy and safety for this dosing approach.

With regard to a non-daily maintenance dosing schedule, the applicant pointed to data from the completed follow-on study ARC004, which explored nondaily maintenance dosing regimens. These data suggest that non-daily maintenance dosing appears not to be as effective as daily dosing in maintaining clinically relevant efficacy and would result in a completely different benefit-risk assessment. Thus, the importance of a daily treatment intake was pronounced.

With regard to modifications of the up-dosing regimen, data from the pivotal studies indicated that only a small proportion of Palforzia-treated subjects needed to reduce their dose or stay at the same dose level on more than one occasion, and the majority of dose reductions or staying at the same dose occurred during the early stages of the up-dosing regimen.

Appropriate dose modification instructions are included in the product information to give the physician to the flexibility to lengthen up-dosing as appropriate for an individual patient per their clinical judgment, although no robust data are available to indicate that fewer adverse reactions would result.

[32] Deschildre A, Elegbede CF, Just J et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. Clin Exp Allergy. 2016 Apr;46(4):610-20. doi: 10.1111/cea.12681.
[33] Blumchen K, Trendelenburg V, Ahrens F et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract. 2019;7(2):479-91.

The amount of peanut protein per dose was analysed within the quality part. However, the dosing regimen is not adjusted according to age, weight or body surface. This might be relevant for efficacy but might be neglectable for safety reasons, because the same dose/dose schedule is applied for adolescents or children, as the doses are increased individually step by step and a possible allergic reaction is monitored carefully.

The dose is applied over a certain time period and the flour is mixed with different foods. Time interval of intake, content of the stomach prior intake, and the food matrix in which the flour is mixed in, and other circumstances are known to influence possible allergic reactions.

2.5.2. Main studies

Study ARC003 - Peanut allergy oral immunotherapy study of Palforzia for desensitization in children and adults (PALISADE)

Methods

Study design

ARC003 phase 3, international, randomised, double-blind, placebo-controlled study evaluated the efficacy and safety of Palforzia in peanut-allergic subjects. The study consisted of screening and double-blind treatment periods that included initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (approximately 24-28 weeks) (Figure 1).

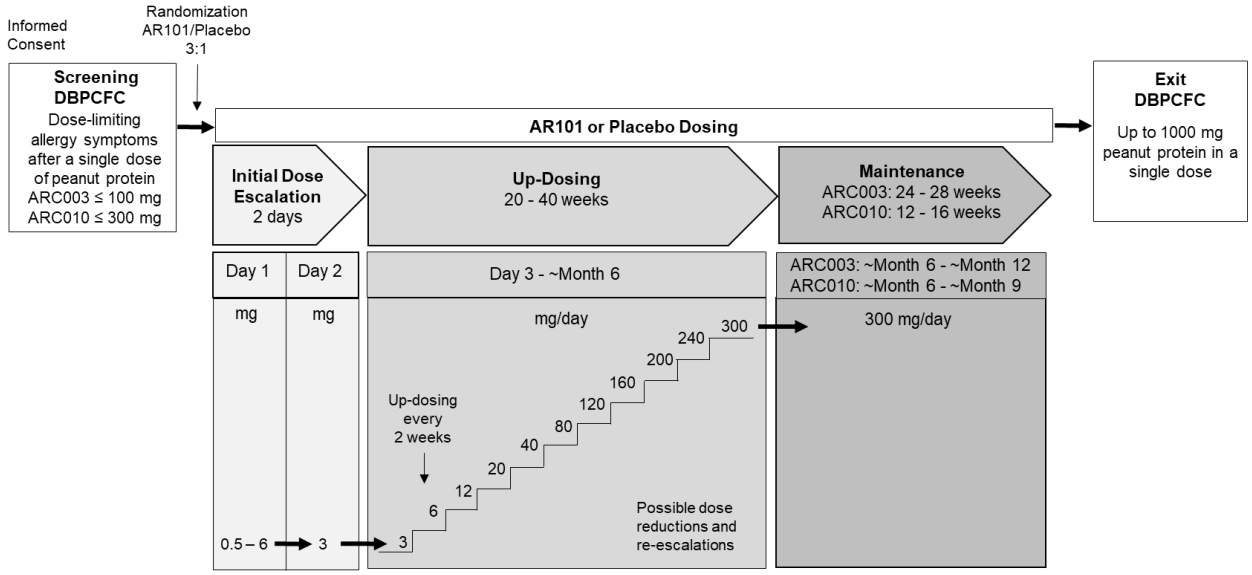


Figure 1 **Study schema (ARC003 and ARC010)**

Study Participants

Inclusion criteria (summary of most notable)

- Subjects aged 4 to 55 years (inclusive);
- Subjects with a clinical history of peanut allergy or peanut-containing foods;

- Subjects with serum IgE to peanut ≥ 0.35 kUA/L and/or a skin prick test to peanut of ≥ 3 mm compared with control at the time of screening;
- Subjects who dose-limiting symptoms (an allergic reaction with type I hypersensitivity symptoms, also called symptoms or allergy symptoms) after consuming a single dose of ≤ 100 mg peanut protein (144 mg cumulative) of food challenge material in a double-blind, placebo-controlled food challenge (DBPCFC) at screening.

Randomisation was stratified by broad geographic region (to include North America and Europe) and age (children aged 4-17 years, inclusive, and adults aged 18-55 years, inclusive).

Exclusion criteria (summary of most notable)

- Subjects with significant cardiovascular disease, intolerance to epinephrine for any reason, of chronic disease (mast cell disorder) and malignancies, a history of severe or life-threatening episode of anaphylaxis or anaphylactic reactions of severe asthma. In addition, patients with a history of eosinophilic GI diseases, including recurrent GI symptoms of undiagnosed etiology were excluded.

Treatments

Treatment with Palforzia was administered in 3 sequential phases: Initial dose escalation, up-dosing, and maintenance. Both the peanut and placebo (oat flour) challenge materials were matched for consistency and taste and mixed with food.

During initial dose escalation on day 1 at the study site, subjects received escalating doses of Palforzia (0.5-6 mg) or placebo at 20- to 30-minute intervals.

On day 2, patients who tolerated at least 3 mg of Palforzia or placebo could initiate the up-dosing phase on day 3.

During up-dosing, subjects received escalating doses from 3 to 300 mg/day of Palforzia or placebo at 2-week intervals as tolerated. The first dose at each new dose level and the first dose of each kit issued during maintenance was given at the study site. Daily dosing continued at home. Study product doses could be reduced, held, or withheld due to adverse events (AEs) or allergy symptoms at investigator discretion.

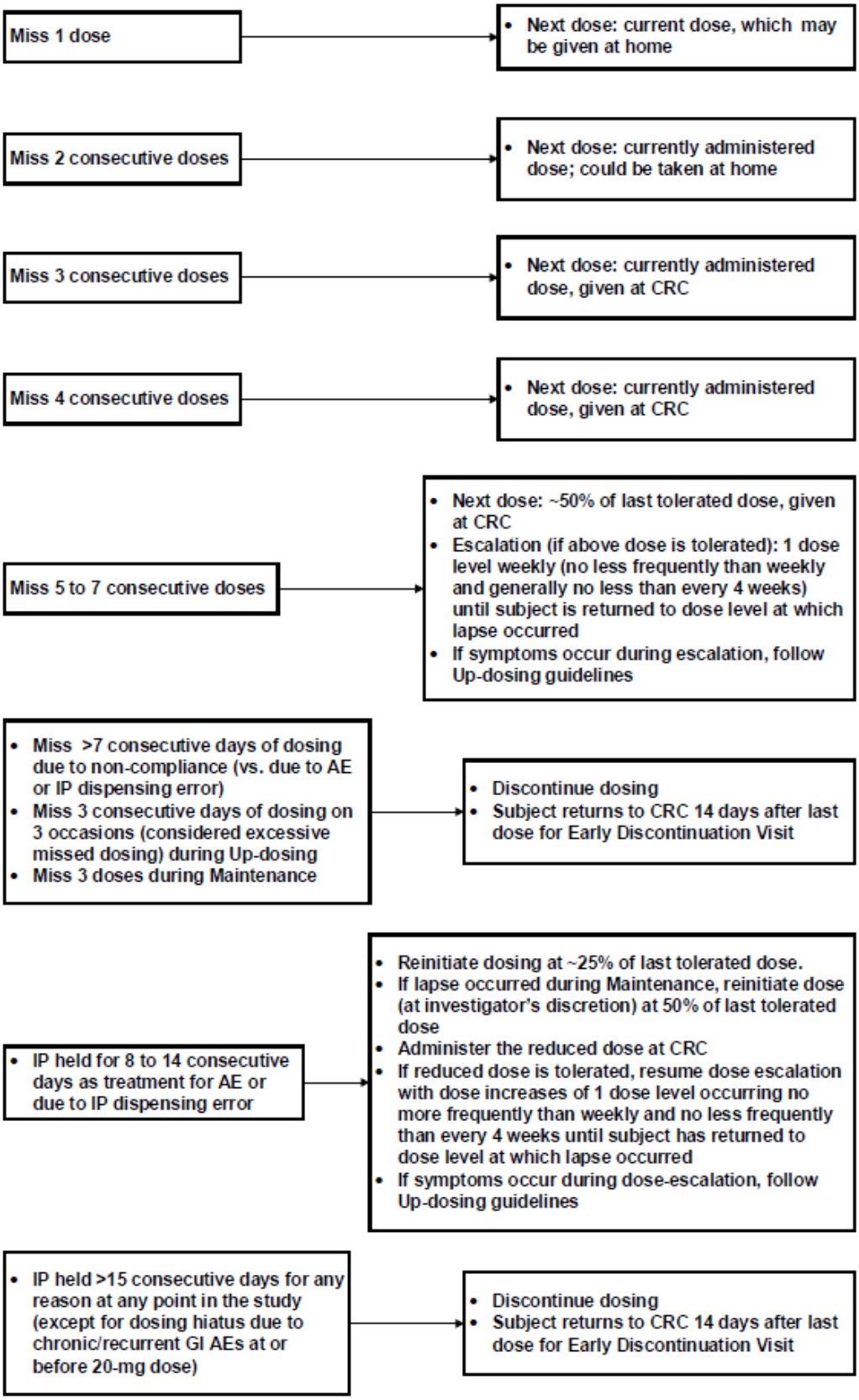
Subjects who tolerated 300 mg/day of Palforzia or placebo continued receiving that dose for maintenance treatment.

The dosing regimen (which is also applicable for study ARC010) is illustrated on Figure 2.

Treatment Administered: Procedures for preparation and administration were the same at the study site or at home. Capsules or sachets containing Palforzia or placebo were emptied into and mixed with a vehicle food supplied by the sponsor (applesauce, pudding) or other palatable, age-appropriate, food (e.g. yogurt). The volume of the vehicle food was to be such that the entire dose could be consumed in a few spoonfuls/mouthfuls in one sitting. Each dose of study product was to be consumed at a consistent time (within 4 hours) each day, with an interval of at least 8 hours between doses.

Dose Modification: Study product doses could be adjusted if the scheduled dose was missed or not tolerated (severity grading of allergic reactions to study product).

Procedures following missed consecutive doses of peanut OIT are presented in Figure 2.



AE= AE; GI=gastrointestinal; CRC=clinical research unit; IP=investigational product

Figure 2 **Procedures Following Missed Consecutive Doses of Peanut OIT**

Objectives

Primary Objectives

- To demonstrate the efficacy of Palforzia, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children aged 4 to 17 years, inclusive

Secondary Objectives

- To demonstrate the safety of Palforzia measured by the incidence of adverse events, including serious adverse events, in children aged 4 to 17 years, inclusive
- To evaluate the immunologic effects of peanut oral immunotherapy (OIT) therapy in children aged 4 to 17 years, inclusive

Outcomes/endpoints

Primary efficacy endpoint:

- The proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulatively) (Europe) and 600 mg peanut protein (1043 mg cumulative) (North America) with no more than mild symptoms at the exit DBPCFC.

Key secondary endpoints:

- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC;
- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC;
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC;
- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC.

Sample size, Randomisation, Blinding (masking)

The sample size for this study (approximately 500 subjects) was selected to provide sufficient power to detect a treatment difference for the primary efficacy analysis. In Europe, the sample size was expected to be adequate to demonstrate a higher desensitisation response rate for the primary efficacy analysis for Palforzia compared with placebo at a significance level of 0.05.

Patients were randomised in a 3:1 ratio to the two treatment arms (Palforzia and placebo). The randomisation was stratified by broad geographic region (North America and Europe) and age (children up to 17 and adults to age 55).

It was a double-blind study. The study as a whole was not planned to be unblinded until after the last subject exits ARC003 and the database is locked. However, patients became de facto unblinded after the Exit DBPCFC as subjects who fail 1 part of the exit food challenge may reasonably deduce that they

were in the placebo arm of the study, and those who tolerate both parts may deduce that they were in the Palforzia arm.

Statistical methods

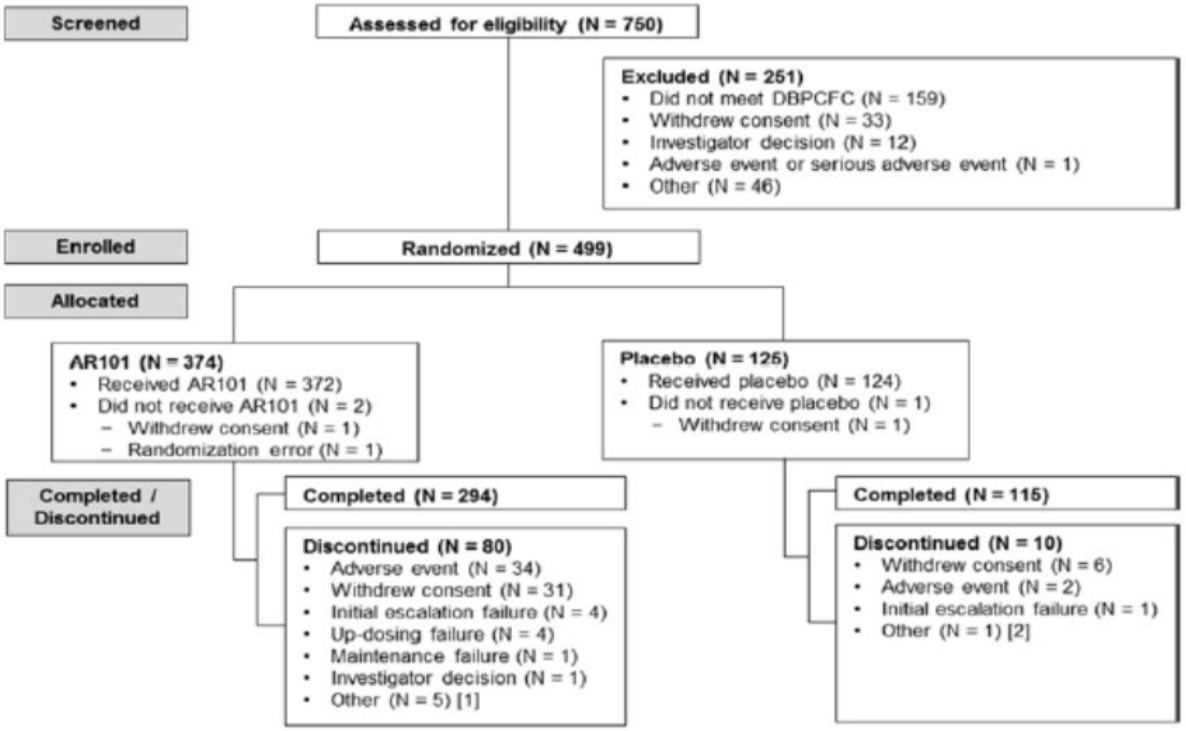
The intention-to-treat (ITT) population was used as the primary analysis population for all analyses of efficacy endpoints. All individuals who dropped out of the study or discontinued OIT prior to undergoing the Exit DBPCFC were considered treatment failures.

Data was summarised descriptively by treatment arm and overall. The descriptive summary for the categorical variables included counts and percentages. The descriptive summary for the continuous variables included means, medians, standard deviations and minimum and maximum values.

The primary endpoint was the proportion of subjects aged 4 to 17 years who achieve desensitisation as determined by tolerating a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC (i.e., responders). The desensitisation response rate and its 95% confidence interval (CI) were calculated for each treatment group with Wilson (score) confidence limits for the binomial proportion. The Farrington-Manning test was used to test that the difference in response rates (Palforzia minus Placebo) was not equal to 0 at the 0.05 significance level. Palforzia was considered to have met primary efficacy endpoint if the lower bound of the corresponding test-based 95% confidence interval is greater than 0.

Results

Participant flow



Source: Table 14.1.1.1, Listing 16.2.1

[1] Reasons included noncompliance for 2 subjects, and relocation, schedule conflict, and randomized in error for 1 subject each.

[2] Subject discontinued due to relocation.

DBPCFC, double-blind, placebo-controlled food challenge.

Figure 3 Subject disposition flow chart (all subjects, 4-17 years) (ARC003)

A total of 750 subjects aged 4 to 17 years were screened. 499 were randomly assigned to study treatment (374 to Palforzia and 125 to placebo).

Of the 374 subjects randomly assigned to Palforzia, 2 did not receive treatment (1 withdrew consent and 1 due to randomisation error). Of the 125 subjects randomly assigned to placebo, 1 withdrew consent before receiving treatment.

A total of 294 of 374 (78.6%) subjects in the Palforzia group and 115 of 125 (92.0%) subjects in the placebo group completed the study. The most common reason for discontinuation of study treatment was subject withdrew consent (31 [8.3%] Palforzia and 6 [4.8%] placebo), followed by adverse event (34 [9.1%] Palforzia and 2 [1.6%] placebo). No subject discontinued the study due to a protocol violation or sponsor decision. No subject died during the study.

Of 21.4% Palforzia-treated and 8.0% placebo-treated subjects who did not complete the study, discontinuation was treatment related for 10.7% of subjects in the Palforzia group and 1.6% of subjects in the placebo group. Chronic or recurrent gastrointestinal (GI) adverse events caused discontinuation for 16 (4.3%) subjects in the Palforzia group and no subjects in the placebo group.

A total of 92 subjects aged 18 to 55 years were screened and 56 were randomly assigned to study treatment (42 to Palforzia and 14 to placebo). Of the 36 (39.1%) subjects who did not pass screening procedures, the primary reason for exclusion from randomisation was that the subject did not meet the screening DBPCFC criterion of dose-limiting symptoms to a single dose of peanut protein ⩽ 100 mg (17 subjects, 18.5%). Thirteen subjects (14.1%) were not randomised for other (not specified) reasons and 6 (6.5%) subjects withdrew consent.

Recruitment

First subject screened: 22 December 2015; First subject dosed: 15 January 2016; Last subject visit: 21 December 2017.

Conduct of the study

The applicant reported 11 amendments protocols (2 global, 2 region-specific, 6 site-specific, and 1 country-specific). The Protocol Amendment 4 (Global) dated 31 July 2017 included the following major changes: Modified the age range (Changed the age range from 4 to 55 years to 4 to 17 years for primary and secondary objectives and clarified that the age range was 4 to 17 years for primary and secondary endpoints, unless specified otherwise.). In addition, the separation of the primary efficacy endpoint for North America and Europe was submitted.

Baseline data
Demographic and Other Baseline Characteristics for Subjects 4 to 17 Years, ITT population

The median age was 9 years and was the same for both treatment groups. Most subjects were male (55.9% Palforzia, 61.3% placebo) and white (78.5%, 78.2%). The proportion of Asian subjects was higher in the Palforzia group (11.0%) compared with the placebo group (6.5%). Black subjects made up less than 2% of the total pediatric population (1.6% Palforzia, 2.4% placebo). Most subjects were enrolled in North America (81.0%) compared with Europe (19.0%); the proportion was similar between treatment groups.

As most subjects in study ARC003 were enrolled in North America (81.0%) compared with Europe (19.0%), the applicant conducted a second Europe-only, efficacy and safety Phase 3 study (ARC010, n=160 subjects; randomised 3:1; age group 4-17 years, see below) to the Palforzia programme.

Baseline Characteristics (ITT population): More than half of subjects in each treatment group had a history of asthma (53.2% Palforzia, 52.4% placebo). About two-thirds of subjects in both treatment groups were allergic to foods other than peanut.

Subjects in both groups had a history of systemic allergic reaction (72.3% Palforzia, 71.8% placebo) and 29.0% in both groups received epinephrine for their most recent reaction.

Baseline median peanut-specific IgE was numerically higher in the placebo group compared with the Palforzia group (68.95 kUA/L Palforzia, 74.80 kUA/L placebo); baseline median peanut-specific IgG4 was similar between treatment groups (0.570 mgA/L Palforzia, 0.610 mgA/L placebo). The median ratio of peanut-specific IgE to IgG4 was higher for the placebo group (155.93) compared with the Palforzia group (131.25).

The median mean wheal diameter in the screening skin prick test to peanut was 11.0 mm for the Palforzia group and 12.0 mm for the placebo group.

Numbers analysed

Table 3 **Analysis populations by treatment group**

Population	Palforzia	Placebo	Total
Safety [1]			
4-17 Years	372 (99.5%)	124 (99.2%)	496 (99.4%)
18-55 Years	41 (97.6%)	14 (100.0%)	55 (98.2%)
4-55 Years	413 (99.3%)	138 (99.3%)	551 (99.3%)
Intent-to-treat [2]			
4-17 Years	372 (99.5%)	124 (99.2%)	496 (99.4%)
18-55 Years	41 (97.6%)	14 (100.0%)	55 (98.2%)
4-55 Years	413 (99.3%)	138 (99.3%)	551 (99.3%)
Completer [3]			
4-17 Years	296 (79.1%)	116 (92.8%)	412 (82.6%)
18-55 Years	20 (47.6%)	13 (92.9%)	33 (58.9%)
4-55 Years	316 (76.0%)	129 (92.8%)	445 (80.2%)
Per protocol [4]			
4-17 Years	289 (77.3%)	113 (90.4%)	402 (80.6%)
18-55 Years	20 (47.6%)	13 (92.9%)	33 (58.9%)
4-55 Years	309 (74.3%)	126 (90.6%)	435 (78.4%)

[1] All subjects who received at least 1 dose of randomised study treatment. Treatment group assignment was based on the treatment received.
[2] All subjects who received at least 1 dose of randomised study treatment. Treatment group assignment was based on the randomised treatment assignment.
[3] All intent-to-treat subjects who completed treatment and had an evaluable exit DBPCFC (completion of at least the peanut food challenge day). (Subjects completing the study had to complete both days of the exit food challenge.)
[4] All subjects in the completer population who had no major protocol deviations that may have influenced the desensitisation response.

Outcomes and estimation

Efficacy Results: Results are presented for the primary study population of subjects aged 4 to 17 years (pediatric subset) and summarised for the ITT population, unless otherwise noted.

The primary efficacy endpoint for study ARC003 was met. Treatment with Palforzia resulted in a statistically significant treatment effect over placebo in the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC after approximately 6 months of maintenance treatment.

Of 372 subjects in the ITT population who received Palforzia, the desensitisation response rate was 50.3% (95% CI: 45.2, 55.3) compared with 2.4% (95% CI: 0.8, 6.9) for the 124 subjects who received placebo. The treatment difference (Palforzia-placebo) was 47.8% (95% CI: 38.0, 57.7; $p < 0.0001$). The results of the primary efficacy endpoint seem conclusive.

The key secondary endpoint - proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC - was met. Treatment with Palforzia resulted in a statistically significant (adjusted for multiplicity) treatment effect over placebo. Of 372 subjects aged 4 to 17 years in the ITT population who received Palforzia, the desensitisation response rate was 67.2% (95% CI: 62.3, 71.8) compared with 4.0% (95% CI: 1.7, 9.1) for 124 subjects who received placebo. The treatment difference (Palforzia-placebo) was 63.2% (95% CI: 53.0, 73.3; $p < 0.0001$).

The secondary efficacy endpoints support the effects seen in the primary endpoint. Results of the secondary efficacy endpoints seem conclusive. Additionally, the high amount of other efficacy endpoints that were assessed support the favourable efficacy compared to placebo.

Only the last key secondary efficacy endpoint of the proportion of adult subjects aged 18 to 55 years in the ITT population (41 Palforzia, 14 placebo) who tolerated a single highest dose of at least 1000 mg peanut protein at the exit DBPCFC was not met. Of 41 subjects aged 18 to 55 years in the ITT population who received Palforzia, the desensitisation response rate was 34.1% (95% CI: 21.6, 49.5) compared with 14.3% (95% CI: 4.0, 39.9) for 14 subjects who received placebo. The treatment difference (Palforzia-placebo) was 19.9% (95% CI: -7.7, 47.4; p=0.1578). In addition, the discontinuation rate was high for adults (about half discontinued early). Reasons for this might be associated with the small number of adults who participated, but may also be associated with other (immunomodulatory) effects and induced side effects. This might be addressed in another trial/another power. Nevertheless the current indication focuses on subjects 4 – 17 years of age. For this age group efficacy has been documented.

With regard to assessments of quality of life (QoL), treatment with Palforzia resulted in similar QoL as measured by subject- and parent-reported the Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) total scores from baseline to exit. This result reflects other literature data on this topic. In addition, a change in QoL aspects needs more time, than the duration of this study – where many subjects experienced an improvement in tolerated amount of peanut protein, but still were blinded and did not "experience" real life situations.

At the request from CHMP, paediatric subgroups in the ITT population were analysed by geographic region (Europe, North America), by age group (4-11 years, 12-17 years), and by region and age group (Europe 4-11 years, 12-17 years; North America 4-11 years, 12-17 years). All performed supportive analyses to the primary efficacy endpoint were consistent with the overall ITT results, except the supportive analysis for the Europe region in the 12 to 17 year age group, which was not statistically significant (tolerated 1000 mg peanut protein: 55.6% Palforzia, 33.3% placebo; treatment difference, 22.2% [95% CI: -37.3, 81.7]; p = 0.4642). This could be explained due to low numbers of participants in the EU region (27 vs 3).

In order to further characterise the populations, who might profit most, the applicant was asked to provide further efficacy data comparing highly allergic individuals with less allergic patients by subdividing patients by degree of severity in peanut-allergic individuals in several subgroups including specific sensitisation levels and baseline food challenge results, as well as age and patients history. Performed analysis according to age revealed robust efficacy data for included subjects aged 4-17 years. From these, a higher response rates in younger children, aged 4-11 years (52.5%) versus older children, aged 12-17 years (46.3%) was observed.

By performing the descriptive sub analyses according to subgroups as defined by IgE, SPT, and DBPCFC, younger, less sensitive subjects, seem to develop the best efficacy rates. However, these descriptive post-hoc sub analysis can only be considered exploratory, as the studies were not designed to investigate such subgroups. In addition, especially in the age group of 12-17 years, sample sizes are too small to enable persistent conclusions.

Ancillary analyses

With regard to concomitant medications during the study, differences between study groups may be mentioned for drugs for the respiratory system (49.2% Palforzia-treated subjects and 38.7% placebo-treated subjects). The use of concomitant medications in adults was comparable to that in pediatric subjects.

Regarding rescue medications, differences mainly occurred during the up-dosing phase and at the exit DBPCFC. At the exit DBPCFC, 31.1% of subjects in the Palforzia group and 89.7% of subjects in the placebo group received any rescue medication; During initial dose escalation and up-dosing, a higher proportion of Palforzia-treated subjects compared with placebo-treated subjects used any rescue medication (69.1% and 48.4%); however, the use of any rescue medication during maintenance was similar between treatment groups (44.5% Palforzia and 41.5% placebo). This trend was generally observed for all ATC classes of rescue medications and generic drug names, except adrenergic and dopaminergic agents (epinephrine) were used by more subjects in the Palforzia group than in the placebo group during both initial dose escalation/up-dosing (10.8% Palforzia and 4.0% placebo) and during maintenance (8.1% and 3.4%).

In the adult subset of the safety population, the overall profile of rescue medication use was similar to that of the pediatric subset during initial dose escalation/up-dosing and maintenance.

Treatment compliance in the pediatric subset was described as approximately 98-99% for both treatment groups during up-dosing and, during maintenance. The mean percentage of planned dosing days where a dose was missed was less than 3% for both treatment groups during both periods (up-dosing and maintenance).

Immunoglobulin values were measured with regard to peanut-specific (ps) IgE and IgG4. The overall trend in ps-IgE in the Palforzia group was an increase from screening to the end of up-dosing and a decrease to the exit DBPCFC whereas values were more or less similar at all time-points in the placebo group. Peanut-specific IgG4 increased from screening to the exit DBPCFC in the Palforzia group and remained similar over time in the placebo. Consequently, the ps-IgE/IgG4 ratio decreased in the Palforzia from screening to exit DBPCFC and was constant in the placebo group.

Study ARC010 - AR101 Trial in Europe Measuring Oral Immunotherapy Success in Peanut Allergic Children (ARTEMIS)

Methods

Study design

ARC010 phase 3, randomised, double-blind, placebo-controlled, multicentre study evaluated the efficacy and safety of Palforzia in peanut-allergic subjects aged 4 to 17 years. The study consisted of screening and double-blind treatment periods that included initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance treatment (approximately 12-16 weeks). The study design is illustrated in ***Figure 4***.. In ARC010 study, the maintenance treatment was shorter than in ARC003 study (ARC010: 12-16 weeks; ARC003: 24-28 weeks).

Study Participants

Inclusion criteria (the most notable)

- Subjects aged 4 – 17 years (inclusive)
- Subjects with clinical history of peanut allergy or peanut-containing foods;
- Subjects with serum i IgE to peanut of ≥ 0.35 kUA/L and/or a peanut skin prick test mean wheal diameter ≥ 3 mm at the time of screening;
- Subjects who had dose-limiting symptoms (type I hypersensitivity symptoms) after consuming ≤ 300 mg peanut protein (444 mg cumulative) food challenge material in a DBPCFC at screening

Exclusion criteria (the most notable)

- Patients with significant cardiovascular disease, intolerance to epinephrine for any reason, of chronic disease (mast cell disorder) and malignancies, a history of severe or life-threatening episode of anaphylaxis or anaphylactic reactions of severe asthma. In addition, patients with a history of eosinophilic GI diseases, including recurrent GI symptoms of undiagnosed etiology were excluded.

Treatments
As in Study ARC003, the treatment with Palforzia was administered in 3 sequential phases: Initial Dose Escalation (first day), up-dosing at 2-week intervals and maintenance. The only difference was the length of the maintenance treatment which was shorter in ARC010 (12-16 weeks).

The dosing regimen is illustrated in ***Figure 4***.

Objectives
The primary objective of study AR010 was to demonstrate the efficacy of Palforzia through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children and adolescents aged 4 to 17 years, inclusive.

The secondary objective was to demonstrate the safety of Palforzia measured by the incidence of adverse events, including serious adverse events and to evaluate the immunologic effects of peanut OIT therapy.

Outcomes/endpoints
The primary endpoint was the proportion of subjects who tolerated a single dose of at least 1000 mg peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC. The primary efficacy endpoint was evaluated using the ITT population.

The key secondary endpoints were:

- Desensitisation response rate at a single dose of 600 mg peanut protein: The proportion of subjects who tolerated a single dose of at least 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC.
- Desensitisation response rate at a single dose of 300 mg peanut protein: The proportion of subjects who tolerated a single dose of at least 300 mg peanut protein (443 mg cumulative) with no more than mild symptoms at the exit DBPCFC.
- The maximum severity of symptoms that occurred at any challenge dose of peanut protein during the exit DBPCFC.

Sample size, Randomisation, Blinding (masking)
The sample size of this study (approximately 160 subjects) was selected to provide sufficient power to detect a treatment difference for the primary efficacy analysis.

Randomisation (Palforzia or placebo 3:1) was performed using an interactive response system on day 1 of initial dose escalation.

This was a double-blind study. Placebo capsules were identical in appearance to the Palforzia capsules and contained excipients color-matched to the peanut flour that were identical to the Palforzia capsules. Matching placebo sachets were also provided for maintenance treatment. Placebo was administered in the same manner as Palforzia.

Statistical methods

The primary endpoint was the proportion of subjects who achieve desensitisation as determined by tolerating 1000 mg as a single dose (2043 mg cumulative) of peanut protein (i.e., a top single challenge dose of 1000 mg) with no more than mild symptoms at the Exit DBPCFC (i.e., responders).

An ITT analysis was performed as the primary efficacy analysis to test for a treatment difference in the response rate. All individuals who drop out of the study or discontinue OIT prior to undergoing the Exit DBPCFC will be considered treatment failures (i.e., Missing = Failure).

Fisher's exact test was planned to be used to test the treatment difference for desensitisation and exact CIs will be constructed as follows: (1) exact Clopper Pearson confidence limits were used for the binomial proportion and (2) exact unconditional confidence limits based on the score statistic were used for the difference in proportions.

The key secondary efficacy endpoints were planned to be tested in the ITT population in hierarchical order.

Each comparison was planned to be evaluated for statistical significance (two-sided $p < 0.05$) only if all of the preceding tests (not including supportive tests) in the hierarchy and the primary analysis of the primary endpoint are statistically significant in favor of Palforzia. Key secondary desensitisation response rates were evaluated for statistical significance using the same analytical methods used for the primary endpoint analysis.

A sensitivity analysis was performed to determine the effect of missing data on the robustness of the primary efficacy endpoint using a worst-case approach to missing data imputation. For subjects with missing data (ie, no exit DBPCFC), placebo-treated subjects were considered responders and Palforzia-treated subjects were considered non-responders.

Results

Participant flow

A total of 175 subjects aged 4 to 17 years were randomly assigned to study treatment (132 to Palforzia and 43 to placebo). Of these, 106 of 132 subjects (80.3%) in the Palforzia group and 40 of 43 subjects (93.0%) in the placebo group completed the study. The most common reason for study discontinuation in the Palforzia group was adverse events or symptoms (14, 10.6%), followed by other (5, 3.8%) and withdrew consent (4, 3.0%). Reasons for study discontinuation in the placebo group were chronic/recurrent GI AEs/symptoms, withdrew consent, and other for 1 subject each (2.3%). The participant flow is presented in ***Figure 4***.

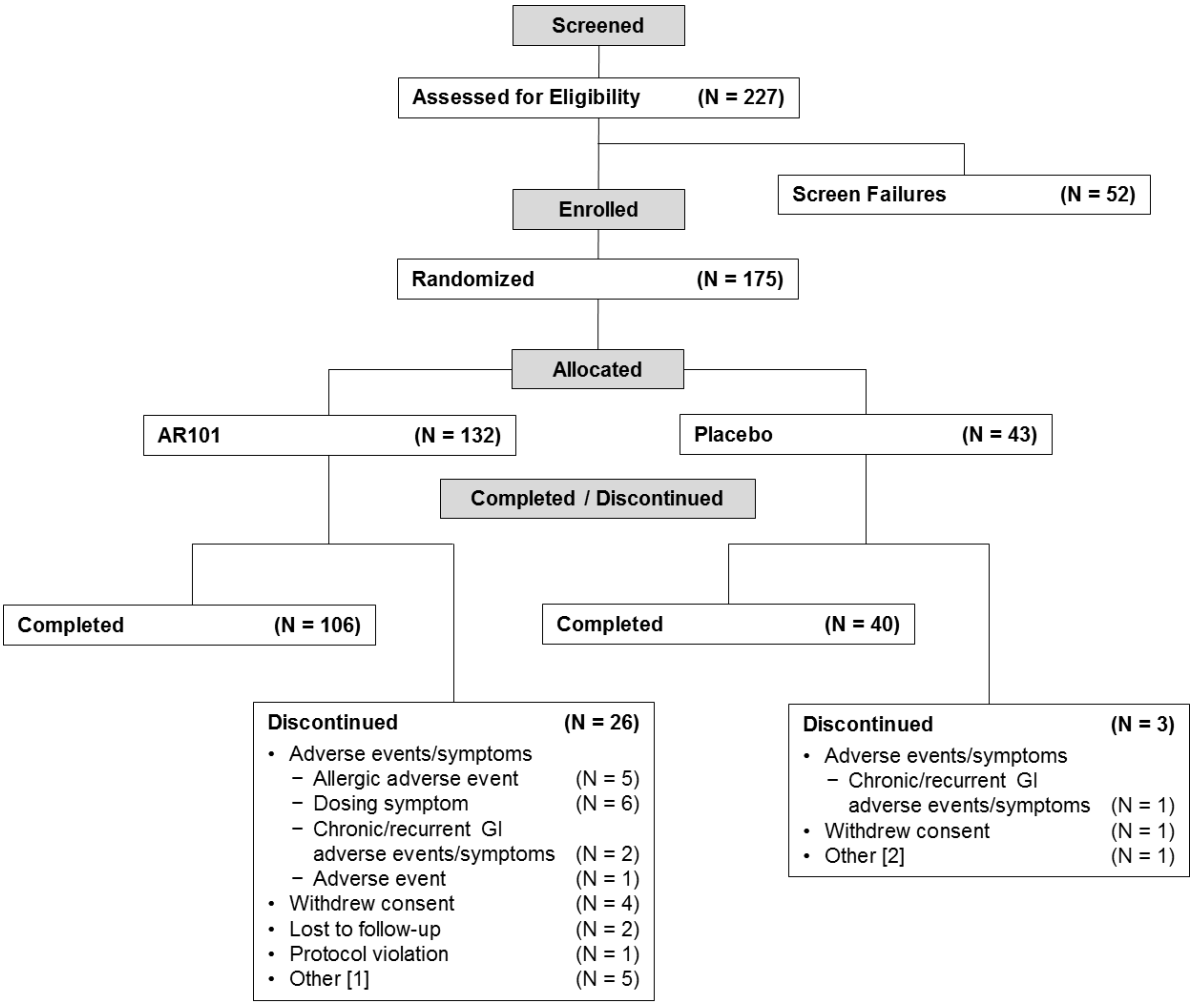


Figure 4 Subject disposition flow chart (all subjects, 4-17 years)

Recruitment

The first subject dose: 26 June 2017; Last subjects visit: 15 February 2019.

Conduct of the study

There were 10 protocol amendments (3 global, 3 site-specific, and 4 country-specific).

With amendment 1 inclusion criterion 3 was modified to remove the upper limit of serum IgE to peanut and include subjects with serum Ig to peanut of at least 35 kUA/L. Amendment 2, among others, modified exclusion criteria and contraception procedure, and added accidental food allergen exposure, severe adverse events, and adverse events associated with epinephrine use as adverse events of interest.

Protocol Amendment 3 clarified - among others- that subjects could continue blinded study treatment in ARC010 if the follow-on study ARC008 was not yet available at the study site.

Major protocol deviation occurred in 21 subjects (15.9%) receiving AR101 and in 9 subjects (20.9&) receiving placebo.

The amendments as well the number and types of protocol deviations are considered acceptable and unlikely to have impacted the results of the study.

Baseline data

For ARC010 study the demographic and baseline characteristics were similar among the treatment groups. Median age of the 175 subjects was 8.0 years (range, 4-17 years). Most subjects in both treatment groups were aged 4 to 11 years (73.5% Palforzia, 69.8% placebo) and more than half were male (51.5%, 62.8%). Most subjects were white (81.8% Palforzia, 81.4% placebo) and were not of Hispanic or Latino ethnicity (90.2%, 90.7%). A total of 40.0% of the overall population reported a history of asthma (42.4% Palforzia, 32.6% placebo).

The median peanut-specific IgG4 (0.3 mgA/L Palforzia, 0.4 mgA/L placebo) and the median ratio of peanut-specific IgE to IgG4 (138.55 AR101, 146.43 placebo) were similar in both groups. The median mean wheal diameter in the screening skin prick test to peanut was similar between treatment groups (9.50 mm Palforzia, 9.75 mm placebo).

Overall, baseline disease characteristics were similar between the placebo and Palforzia treatment groups and mean baseline values for all assessments were consistent.

Numbers analysed

Table 4 Analysis Populations by Treatment Group

Population	Palforzia	Placebo	Total
Safety [1]			
4-17 Years	132 (100%)	43 (100%)	175 (100%)
4-11 Years	97 (100%)	30 (100%)	127 (100%)
12-17 Years	35 (100%)	13 (100%)	48 (100%)
Intent-to-treat [2]			
4-17 Years	132 (100%)	43 (100%)	175 (100%)
4-11 Years	97 (100%)	30 (100%)	127 (100%)
12-17 Years	35 (100%)	13 (100%)	48 (100%)
Completer [3]			
4-17 Years	106 (80.3%)	40 (93.0%)	146 (83.4%)
4-11 Years	82 (84.5%)	27 (90.0%)	109 (85.8%)
12-17 Years	24 (68.6%)	13 (100%)	37 (77.1%)
Per protocol [4]			
4-17 Years	90 (68.2%)	33 (76.7%)	123 (70.3%)
4-11 Years	70 (72.2%)	22 (73.3%)	92 (72.4%)
12-17 Years	20 (57.1%)	11 (84.6%)	31 (64.6%)

[1] All subjects who received at least 1 dose of randomised study treatment (not including food challenge material administered during DBPCFCs). Treatment group assignment was based on the treatment received.

[2] All subjects who received at least 1 dose of randomised study treatment. Treatment group assignment was based on the randomised treatment assignment.

[3] All intent-to-treat subjects who completed treatment and had an evaluable exit DBPCFC (completion of at least the peanut food challenge day). (Subjects completing the study had to complete both days of the exit food challenge.)

[4] All subjects in the completer population who had no major protocol deviations that may have influenced the desensitisation response.

Outcomes and estimation

In study ARC010 all prespecified primary and key secondary endpoints of desensitisation response (1000 mg, 600 mg, 300 mg) and maximum severity of symptoms at any challenge dose of peanut protein during the exit DBPCFC in the ITT population were met. The treatment with Palforzia resulted in a statistically significant treatment effect over placebo in the proportion of subjects aged 4 to 17 years who tolerated a single dose of at least 1000 mg peanut protein (2043 mg cumulative). Of 132 subjects in the ITT population who received Palforzia, the desensitisation response rate was 58.3%

(95% CI: 49.4, 66.8) compared with 2.3% (95% CI: 0.1, 12.3) for 43 subjects who received placebo. The treatment difference (Palforzia-placebo) was 56.0% (95% CI: 44.1, 65.2); p < 0.0001.

Key secondary endpoints:

Desensitisation response rate at a single dose of 1000 mg peanut protein (2043 mg cumulative): 58.3% Palforzia and 2.3% placebo; treatment difference, 56.0% (95% CI: 44.1, 65.2; p < 0.0001)

Desensitisation response rate at a single dose of 600 mg peanut protein (1043 mg cumulative): 68.2% Palforzia and 9.3% placebo; treatment difference, 58.9% (95% CI: 44.2, 69.3; p < 0.0001)

Desensitisation response rate at a single dose of 300 mg peanut protein (443 mg cumulative): 73.5% Palforzia and 16.3% placebo; treatment difference, 57.2% (95% CI: 41.2, 69.1; p < 0.0001)

A clinically meaningful reduction in the maximum severity of symptoms at any challenge dose of peanut protein was observed at the exit DBPCFC for the Palforzia group compared with the placebo group (p < 0.0001). Palforzia treatment resulted in immunologic changes throughout the study as demonstrated by changes in peanut-specific IgE, IgG4, IgE/IgG4 ratio, and mean wheal diameter in the skin prick test from baseline to study exit.

These results are consistent with the results of the pivotal study ARC003 conducted in Europe and North America.

At the request from CHMP, supportive analyses to the primary efficacy endpoint for study ARC010 were performed. Treatment differences (Palforzia-placebo) were consistent with the primary efficacy endpoint for the regional populations by country in countries that enrolled a sufficient number of subjects. Subgroup analyses by age group (4-11 years, 12-17 years) for the primary efficacy endpoint were also consistent with the overall ITT results; however, the treatment difference was less, but still statistically significant for the smaller age group of 12 to 17 years. Among patients aged 4-11 years, 52-60% tolerated 1000 mg peanut protein, while 45-46% patients aged 12-17 years and 34% of patients aged 18-55 years met this endpoint at the exit DBPCFC.

In order to further characterise the populations, who might profit most, the applicant was asked to provide further efficacy data comparing highly allergic individuals with less allergic patients by subdividing patients by degree of severity in peanut-allergic individuals in several subgroups including specific sensitisation levels and baseline food challenge results, as well as age and patients history. Performed analysis according to age revealed robust efficacy data for included subjects aged 4-17 years. From these, a higher response rates in younger children, aged 4-11 years (62.9%) versus older children, aged 12-17 years (45.7%) was observed. Interestingly, the highest response rate (62.9%) was reached in children aged 4-11 years in the European only study ARC010, although their treatment maintenance phase was half as long as in ARC003. This may be associated with slightly different inclusion criteria (leading to "some less sensitive subjects" being included), but it may also support the impact of "age", as included children were slightly younger in ARC010 (median 8 years).

By performing the descriptive sub analyses according to subgroups as defined by IgE, SPT, and DBPCFC, younger, less sensitive subjects, seem to develop the best efficacy rates. However, these descriptive post-hoc sub analysis can only be considered exploratory, as the studies were not designed to investigate such subgroups. In addition, especially in the age group of 12-17 years, sample sizes are too small to enable persistent conclusions.

Ancillary analyses

The primary efficacy analysis was repeated for the ITT population age subgroups of 4 to 11 years and 12 to 17 years. The results were consistent with the overall population although the treatment difference was less for the much smaller age group of 12 to 17 years (35 Palforzia, 13 placebo; 45.7%

[95% CI: 28.8, 63.4]; p = 0.0033) compared with 4 to 11 years (97 Palforzia, 30 placebo; 62.9% [95% CI: 52.5, 72.5]; p < 0.0001).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 5 Summary of Efficacy for trial ARC003

Title: Peanut Allergy Oral Immunotherapy Study of Palforzia for Desensitisation in Children and Adults (PALISADE)			
Study identifier	ARC003 NCT02635776 2015-004257-41		
Design	International, multicentre, randomised, double-blind, placebo-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 12 months (44-68 weeks)
Hypothesis	Superiority		
Treatments groups	Palforzia		Initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (24-28 weeks) with Palforzia randomization 3:1
	Placebo		Initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (24-28 weeks) with Placebo
Endpoints and definitions	Primary endpoint	1000 mg peanut challenge, 4-17y	Proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least **1000** mg peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC
	Key Secondary endpoints	600 mg peanut challenge, 4-17y	Proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least **600** mg (1043 mg cumulative)
		300 mg peanut challenge, 4-17y	Proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least **300** mg (443 mg cumulative)

		Max severity symptoms	Maximum severity of symptoms in subjects aged 4 to 17 years that occurred at any challenge
		1000 mg peanut challenge, 18-44y	Proportion of subjects aged 18 to 55 years who tolerated a single highest dose of at least **1000** mg (2043 mg cumulative)
Database lock	26 Jan 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary efficacy endpoints were evaluated using the intent-to-treat (ITT) population with patients received at least one dose. Primary study population of subjects aged 4 to 17 years		
Descriptive statistics and estimate variability	Treatment group	Palforzia	Placebo
	ITT - Number of subject, 4-17y	372	124
	1000 mg peanut challenge, 4-17y, response rate	50.3%	2.4%
	(95% CI)	(45.2, 55.3)	(0.8, 6.9)
	600 mg peanut challenge, 4-17y, response rate	67.2%	4.0%
	(95% CI)	(62.3, 71.8)	(1.7, 9.1)
	300 mg peanut challenge, 4-17y, response rate	76.6%	8.1%
	(95% CI)	(72.1, 80.6)	(4.4, 14.2)
	Max severity symptoms		
	None, n (%)	140 (37.6%)	3 (2.4%)
	Mild, n (%)	119 (32.0%)	35 (28.2%)
	Moderate, n (%)	94 (25.3%)	73 (58.9%)
	Severe, n (%)	19 (5.1%)	13 (10.5%)
	ITT - Number of subject, 18-55y	41	14
	1000 mg peanut challenge, 18-55y, response rate	34.1%	14.3%
	(95% CI)	(21.6, 49.5)	(4.0, 39.9)

Effect estimate per comparison		Comparison groups	Active - Placebo
	1000 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	47.8%
		95% CI	(38.0, 57.7)
		P-value	<0.0001
	600 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	63.2%
		95% CI	(53.0, 73.3)
		P-value	<0.0001

	300 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	68.5%
		95% CI	(58.6, 78.5)
		P-value	<0.0001
	Max severity symptoms	P-value	<0.0001
	1000 mg peanut challenge, 18-55y	Treatment difference (Palforzia-placebo)	19.9%
		95% CI	(-7.7, 47.4)
		P-value	0.1578
Notes	Based on the primary endpoint and key secondary endpoints the study shows that within the age group of 4-17 years old patients with an allergy against peanut protein the symptoms attenuate significantly towards mild or no symptoms.		

Table 6 Summary of Efficacy for trial ARC010

Title: Palforzia Trial in Europe Measuring Oral Immunotherapy Success in Peanut Allergic Children (ARTEMIS)			
Study identifier	ARC010 NCT03201003 2016-005004-26		
Design	Phase 3, randomised, double-blind, placebo-controlled Maintenance: ~3 months		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 12 months (44-68 weeks) Not applicable Nor applicable
Hypothesis	Superiority		
Treatments groups	AR101		Initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (20-40 weeks) with Palforzia
	Placebo		Initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (20-40 weeks) with Placebo
Endpoints and definitions	Primary endpoint	1000 mg peanut challenge	Efficacy: Proportion of subjects who achieve desensitisation (tolerate a single dose of at least 1000 mg [2043 mg cumulative] peanut protein with no more than mild symptoms at the exit DBPCFC)

	Key Secondary endpoints - evaluated in hierarchical order as if primary efficacy endpoint was significant at the 0.05 level	600 mg peanut challenge	Proportion of subjects who tolerated a single dose of at least 600 mg peanut protein (1043 mg cumulative)
		300 mg peanut challenge	Proportion of subjects who tolerated a single dose of at least 300 mg peanut protein (443 mg cumulative)
		Max severity of symptoms	The maximum severity of symptoms that occurred at any challenge dose during exit DBPCFC
Database lock	07.03.2019		
Results and Analysis			

Analysis	**Primary Analysis**		
Analysis population and time point description	The primary efficacy endpoint was evaluated using the ITT population.		
Descriptive statistics and estimate variability	Treatment group	Palforzia	Placebo
	ITT - Number of subject	132	43
	1000 mg peanut challenge, response rate	58.3%	2.3%
	(95% CI)	(49.4, 66.8)	(0.1, 12.3)
	600 mg peanut challenge, response rate	68.2%	9.3%
	(95% CI)	(59.5, 76.0)	(2.6, 22.1)
	300 mg peanut challenge, response rate	73.5%	16.3%
	(95% CI)	(65.1, 80.8)	(6.8, 30.7)
	Max severity symptoms		
	None, n (%)	47 (35.6%)	0
	Mild, n (%)	55 (41.7%)	16 (37.2%)
	Moderate, n (%)	24 (18.2%)	20 (46.5%)
	Severe, n (%)	6 (4.5%)	7 (16.3%)

Effect estimate per comparison		Comparison groups	Active - Placebo
	1000 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	56.0%
		95% CI	(44.1, 65.2)
		P-value	<0.0001
	600 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	58.9%
		95% CI	(44.2, 69.3)
		P-value	<0.0001
	300 mg peanut challenge, 4-17y	Treatment difference (Palforzia-placebo)	57.2%
		95% CI	(41.2, 69.1)
		P-value	<0.0001
	Max severity symptoms	P-value	<0.0001
Notes	The primary and key secondary endpoints were met.		

2.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Overall summary results for ARC003 and ARC001 studies

No pooled analyses, respectively meta-analysis was possible. Nevertheless, central aspects between the 2 pivotal phase 3 studies ARC003 and ARC010 overlap. ARC003 was a large, randomised, double-blind, placebo-controlled study of Palforzia in subjects with peanut allergy aged 4 to 55 years conducted in Europe and North America. ARC010 was a phase 3, randomised, double-blind, placebo-controlled, multicentre study of Palforzia in subjects with peanut allergy aged 4 to 17 years conducted in Europe.

In both studies, subjects were randomly assigned to blinded treatment 3:1 (Palforzia to placebo) to ensure that subject populations were similar in the test and control groups and to eliminate bias. Efficacy data from these studies were not integrated for this application due to differences in study eligibility requirements and study duration. As studies ARC003 and ARC010 differed in certain points, a direct comparison of results is not possible.

Table 7 Overall Summary of Primary and Key Secondary Efficacy Endpoints for Study ARC003 and Study ARC010 (ITT Population)

Endpoint	ARC003		ARC010	
	Palforzia	**Placebo**	**Palforzia**	**Placebo**
Subjects Aged 4-17 y, n	N = 372	N = 124	N = 132	N = 43
Primary Efficacy Endpoint				
Response rate: proportion of subjects 1000 mg peanut protein at the exit DBPCFC (95% CI), 4-17 y [1]	50.3% (45.2, 55.3)	2.4% (0.8, 6.9)	58.3% (49.4, 66.8)	2.3% (0.1, 12.3)
Treatment difference (Palforzia-placebo) [95% CI] [2]	47.8% (38.0, 57.7)		56.0% (44.1, 65.2)	
P-value [2]	< 0.0001		< 0.0001	
Key Secondary Efficacy Endpoints				
Response rate: proportion of subjects 600 mg peanut protein at the exit DBPCFC (95% CI), 4-17 y [1]	67.2% (62.3, 71.8)	4.0% (1.7, 9.1)	68.2% (59.5, 76.0)	9.3% (2.6, 22.1)
Treatment difference (Palforzia-placebo) [95% CI] [2]	63.2% (53.0, 73.3)		58.9% (44.2, 69.3)	
P-value [2]	< 0.0001		< 0.0001	
Response rate: proportion of subjects of 300 mg peanut protein at the exit DBPCFC (95% CI), 4-17 y [1]	76.6% (72.1, 80.6)	8.1% (4.4, 14.2)	73.5% (65.1, 80.8)	16.3% (6.8, 30.7)
Treatment difference (Palforzia-placebo) [95% CI] [2]	68.5% (58.6, 78.5)		57.2% (41.2, 69.1)	
P-value [2]	< 0.0001		< 0.0001	
Maximum severity of symptoms at any peanut challenge dose at the exit DBPCFC, 4-17 y [3]				
None	140 (37.6%)	3 (2.4%)	47 (35.6%)	0
Mild	119 (32.0%)	35 (28.2%)	55 (41.7%)	16 (37.2%)
Moderate	94 (25.3%)	73 (58.9%)	24 (18.2%)	20 (46.5%)
Severe or higher [4]	19 (5.1%)	13 (10.5%)	6 (4.5%)	7 (16.3%)
P-value [5]	< 0.0001		< 0.0001	
Subjects Aged 18-55 y, n	N = 41	N = 14	na	na
Response rate: proportion of subjects 1000 mg peanut protein at the exit DBPCFC (95% CI), 18-55 y [1]	34.1% (21.6, 49.5)	14.3% (4.0, 39.9)	na	na
Treatment difference (Palforzia-placebo) [95% CI] [2]	19.9% (-7.7, 47.4)		na	
P-value [2]	0.1578		na	

Subjects without an exit DBPCFC were counted as nonresponders.
[1] ARC003: Based on Wilson (score) confidence limits.

ARC010: Based on exact Clopper-Pearson intervals.
[2] ARC003: Treatment difference and p-value were based on the Farrington-Manning confidence limits.
ARC010: Treatment difference was based on exact unconditional confidence limits using the score statistic. P-value was based on the Fisher exact test.
[3] Subjects without an exit DBPCFC were assigned the maximum severity of symptoms during the screening DBPCFC (no change from screening).
[4] No subjects had symptoms considered life-threatening or fatal.
[5] Tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region (Europe, North America) for ARC003 and by country for ARC010.

Use of Epinephrine as Rescue Medication in DBPCFCs

The proportion of subjects with any epinephrine use during the peanut challenge day of the screening DBPCFC was higher in ARC003 compared with ARC010 (~36.4% vs ~20.5%), possibly due to different rates of epinephrine use in Europe compared with North America.

In both ARC003 and ARC010, the overall use of epinephrine during the peanut challenge day of the exit DBPCFC was less frequent for subjects treated with Palforzia compared with placebo.

Table 8 Epinephrine Use as Rescue Medication During the DBPCFCs (Completer Population, 4-17 Years)

	ARC003		ARC010	
	Palforzia (N = 296)	**Placebo (N = 116)**	**Palforzia (N = 106)**	**Placebo (N = 40)**
Subjects with any epinephrine use as rescue medication during the screening DBPCFC				
Placebo challenge				
Yes	0	0	0	0
No	296 (100.0%)	116 (100.0%)	106 (100%)	40 (100%)
Peanut challenge				
Yes	107 (36.1%)	43 (37.1%)	22 (20.8%)	8 (20.0%)
No	189 (63.9%)	73 (62.9%)	84 (79.2%)	32 (80.0%)
Subjects with any epinephrine use as rescue medication during the exit DBPCFC				
Placebo challenge				
Yes	1 (0.3%)	0	0	0
No	293 (99.0%)	116 (100.0%)	106 (100%)	40 (100%)
P-value [1]	> 0.9999		Not calculable	
Peanut challenge				
Yes	28 (9.5%)	62 (53.4%)	3 (2.8%)	7 (17.5%)
No	268 (90.5%)	54 (46.6%)	103 (97.2%)	33 (82.5%)
P-value [1]	< 0.0001		0.0046	

Changes in Peanut-Specific IgE and IgG4

The change from baseline in immunoglobulin values was evaluated for subjects aged 4 to 17 years in the ITT and completer populations of ARC003 and ARC010. In both studies, the overall trend in peanut-specific IgE in the Palforzia group was an increase from screening to the end of up-dosing and a decrease to the exit DBPCFC. The overall trend in peanut-specific IgE in the placebo group was an increase from screening to the end of up-dosing and a small decrease or no change to the exit DBPCFC. Peanut-specific IgG4 increased and the peanut-specific IgE/IgG4 ratio decreased from screening to exit for the Palforzia group compared with the placebo group.

Changes in Peanut Skin Prick Test

For subjects aged 4 to 17 years in the ITT population of both ARC003 and ARC010, the mean wheal diameter in the skin prick test decreased overall from baseline to study exit for the Palforzia group compared with the placebo group. The mean (SD) wheal diameter was similar between treatment groups at baseline and was decreased at the end of up-dosing (300 mg visit) and at study exit for the Palforzia group compared with the placebo group. The change from baseline to exit in mean (SD) wheal diameter was greater for the Palforzia group compared with the placebo group.

The applicant described, that similar treatment effects were observed in the phase 2 studies ARC001 and ARC002.

2.5.4. Clinical studies in special populations

Children

Palforzia was mainly investigated in children (1-17 yrs) as the marketing authorisation is sought for this age group. Limited data is available in adults (> 18 years of age). No data are available for the elderly population.

Subjects who turn age 18 years during Palforzia treatment

Among subjects who completed studies ARC003, ARC004, and ARC010, 14 subjects reached age 18 years before completing the exit DBPCFC. Of these 14 subjects, 9 were treated with Palforzia (ARC003 (9 subjects; 5 Palforzia, 4 placebo), ARC004 (4 subjects; all Palforzia), and ARC010 (1 subject; placebo)). In ARC003, 4 of 5 subjects who reached age 18 years after beginning Palforzia treatment tolerated a single highest dose of 1000 mg peanut protein with no more than mild symptoms during the ARC003 exit DBPCFC, compared with 0 of 4 placebo-treated subjects. All 4 Palforzia-treated subjects who reached age 18 years during study ARC004 tolerated a single highest dose of 1000 mg peanut protein with no more than mild symptoms during the ARC003 exit DBPCFC, and clinically meaningful desensitization was maintained after an additional approximately 28 weeks of Palforzia treatment: 2 subjects tolerated a single highest dose of 2000 mg peanut protein, 1 subject tolerated 1000 mg peanut protein, and 1 subject tolerated 600 mg peanut protein with no more than mild symptoms during the ARC004 exit DBPCFC. The placebo-treated subject in ARC010 who reached age 18 years had a single highest tolerated dose of 1 mg at the exit DBPCFC.

During the evaluation, the applicant provided an updated data set and reported of n = 51 patients, which were enrolled at age ≤ 17 years and subsequently turned age 18 during treatment with Palforzia (enrolled in different studies: ARC003, ARC010, ARC0101 respectively in follow-on studies ARC004 and ARC008). From these 51 patients nearly two-thirds of the subjects who turned age 18 during Palforzia treatment (33 subjects, 64.7%) remain ongoing in the follow-on study ARC008. From the limited efficacy data which were available for 27 of these patients the applicant assumed that the general profile of efficacy is similar to other age groups.

2.5.5. Supportive studies

ARC004 – Peanut Allergy Oral Immunotherapy Study of Palforzia for Desensitization in Children and Adults (PALISADE) Follow-On Study

ARC004 was an international, multicentre, open-label, 2-arm follow-on Phase 3 study to ARC003 designed to allow subjects who received placebo in ARC003 the opportunity to receive Palforzia and to evaluate the safety, tolerability and efficacy of Palforzia in children and adults with peanut allergy.

The final clinical study report (CSR) ARC004 (finalised 14 Feb 2020) was submitted with the responses to the D120 list of questions. An overview of the ARC004 study design, disposition of subjects aged 4 to 17 years, and key conclusions with supporting data are described below.

Study Design

Subjects who completed placebo treatment in ARC003 and subjects who received Palforzia and tolerated ≥ 300 mg peanut protein (443 mg cumulative) at the ARC003 exit DBPCFC could enroll in ARC004. Treatment paths for this open-label follow-on study were as follows:

Group 1 (placebo-treated subjects in ARC003): Subjects received Palforzia during IDE (day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up-dosing (3-300 mg/day for 22-40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24-28 weeks). A DBPCFC after approximately 6 months of maintenance treatment evaluated up to a single highest dose of 2000 mg peanut protein food challenge material (4043 mg cumulative). Subjects who tolerated a single highest dose of at least 300 mg in the DBPCFC could receive Palforzia during extended maintenance in gradually increasing dosing intervals depending on the results from group 2. The total duration of Palforzia treatment in group 1 was 88 to 136 weeks.

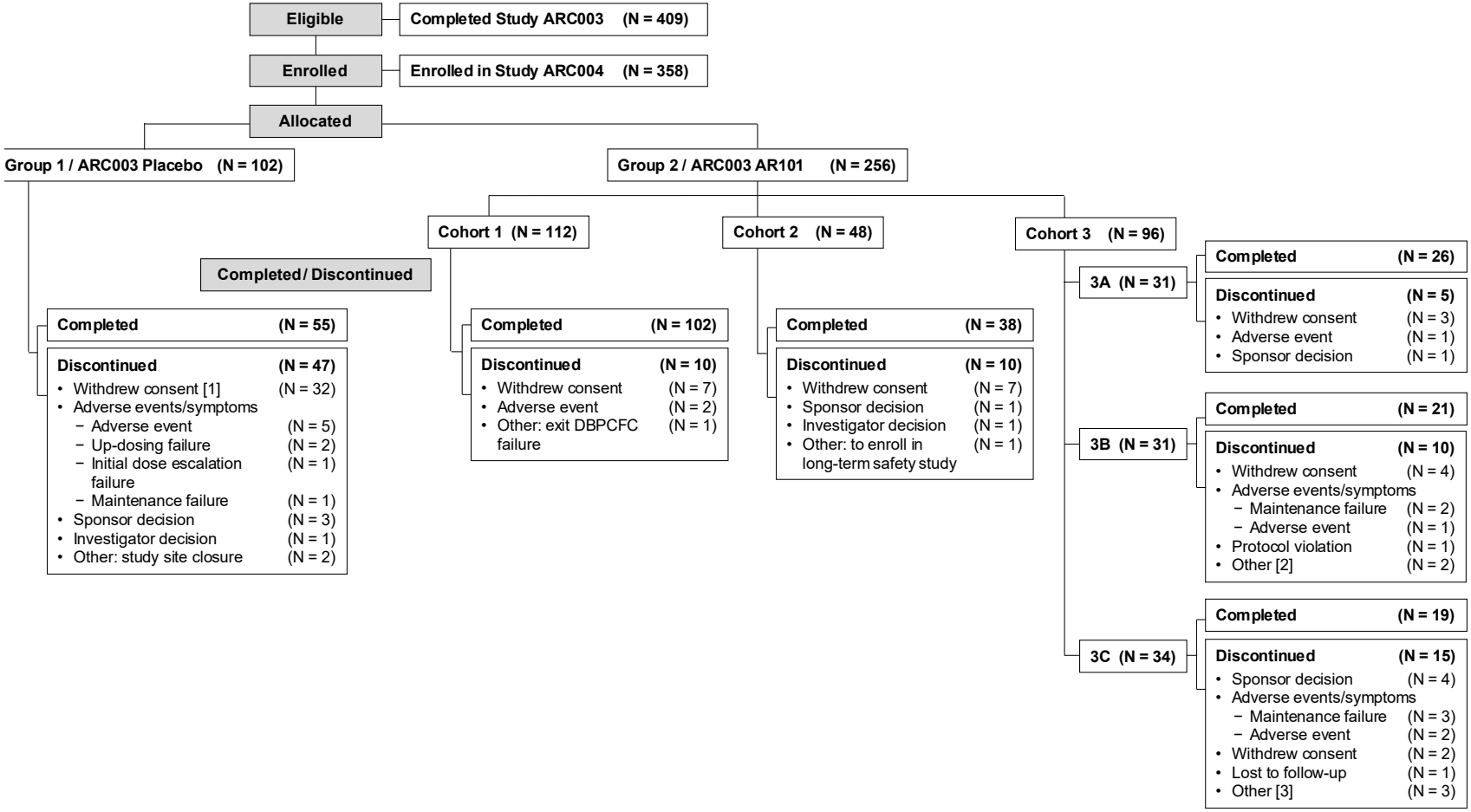
Group 2 (Palforzia-treated subjects who tolerated ≥ 300 mg peanut protein in the exit DBPCFC in ARC003): Subjects were assigned to 1 of 3 sequential dose cohorts in group 2. The first approximately 120 subjects received 300 mg/day (once daily, QD) for 28 weeks in cohort 1. The next approximately 50 subjects received 300 mg every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks in cohort 2. All remaining subjects were assigned to 1 of 3 dosing regimens in cohort 3:

- Cohort 3A: 300 mg/day for 56 weeks
- Cohort 3B: 300 mg/day for 28 weeks, QOD for 4 weeks, then BIW for 24 weeks (total of 56 weeks)
- Cohort 3C: 300 mg/day for 28 weeks, QOD for 4 weeks, BIW for 24 weeks, then once weekly (QW) for 28 weeks (total of 84 weeks)

Disposition of Subjects

A total of 358 subjects aged 4 to 17 years who completed study ARC003 were enrolled and 351 subjects were treated with Palforzia in study ARC004: 102 were enrolled in group 1 (former placebo) and 256 in group 2 (former Palforzia). Group 2 was further divided into cohorts (112 subjects in cohort 1, 48 in cohort 2, 31 in cohort 3A, 31 in cohort 3B, 34 in cohort 3C).

In group 1, 55 of 102 subjects (53.9%) completed the study. In group 2, 206 of 256 subjects (80.5%) completed the study (102 subjects in cohort 1, 38 in cohort 2, 26 in cohort 3A, 21 in cohort 3B, 19 in cohort 3C); completion rates were higher for cohorts with only QD dosing (83.9%-91.1%) than nondaily dosing (55.9%-79.2%). Reasons for discontinuation are summarised in the subject disposition flow chart.



[1] Data entry error. One subject was marked as completing the ARC004 exit DBPCFC but withdrew consent before receiving AR101 and was not counted in the safety or completer populations.
[2] Reasons included exit DBPCFC failure and reverted to QD dosing for 1 subject and recurrent adverse events for 1 subject.
[3] Reasons included anxiety related to dosing, no longer interested in participating in study, and study termination for 1 subject each.
DBPCFC, double-blind, placebo-controlled food challenge; QD, once daily.

Figure 5 : Subject Disposition Flow Chart (All Subjects, 4-17 Years)

Results

Considering the low number of participants per group, the applicant summarised following Key Study Conclusions:

The key efficacy, safety, immunomodulation, and quality of life conclusions are presented for subjects aged 4 to 17 years at time of enrolment in ARC004.

Efficacy: longer duration of once daily (QD) dosing was associated with maintained or improved effectiveness of desensitisation.

- Progressive desensitisation over time was observed in subjects with up to 18 months of Palforzia dosing at 300 mg/day, with no indication of a plateaued response with longer-term dosing.
- Desensitisation response rates at the exit DBPCFC were consistently high between groups and across cohorts at each challenge dose of peanut protein (300, 600, 1000, 2000 mg), and were generally higher for group 1 (former placebo) and the group 2 cohorts with only QD dosing (28- and 56-week schedules) than for the cohorts that included nondaily every other day (QOD) and twice weekly (BIW) dosing.
- The greatest single highest tolerated dose increased from screening (baseline) to the exit DBPCFC, particularly in cohorts with only QD dosing, consistent with ongoing immunomodulatory effects of OIT and suggesting that desensitisation is better maintained and may improve over time with steady QD dosing compared with nondaily QOD and BIW dosing.
- Epinephrine use at any peanut challenge dose in the exit DBPCFC was lowest in the cohort with the longest dosing schedule (56 weeks).

Table 9: Desensitisation Response Rates at the Exit DBPCFC (Completer Population, 4-17 Years)

		Group 2				
	Group 1 (N = 72)	**Cohort 1 (N = 103)**	**Cohort 2 (N = 38)**	**Cohort 3A (N = 26)**	**Cohort 3B (N = 22)**	**Cohort 3C (N = 21)**
Single highest tolerated dose with no more than mild symptoms at exit DBPCFC						
3 mg	0	0	0	0	0	0
10 mg	0	0	0	0	0	0
30 mg	0	2 (1.9%)	1 (2.6%)	0	0	0
100 mg	1 (1.4%)	0	1 (2.6%)	0	4 (18.2%)	2 (9.5%)
300 mg	9 (12.5%)	9 (8.7%)	9 (23.7%)	1 (3.8%)	1 (4.5%)	3 (14.3%)
600 mg	10 (13.9%)	9 (8.7%)	5 (13.2%)	0	2 (9.1%)	2 (9.5%)
1000 mg	15 (20.8%)	33 (32.0%)	8 (21.1%)	4 (15.4%)	5 (22.7%)	5 (23.8%)
2000 mg	37 (51.4%)	50 (48.5%)	14 (36.8%)	21 (80.8%)	10 (45.5%)	9 (42.9%)
Subjects who tolerated a single dose of 300 mg peanut protein (response rate)	71 (98.6%)	101 (98.1%)	36 (94.7%)	26 (100%)	18 (81.8%)	19 (90.5%)
(95% CI)	(92.5%, 100%)	(93.2%, 99.8%)	(82.3%, 99.4%)	(86.8%, 100%)	(59.7%, 94.8%)	(69.6%, 98.8%)
Subjects who tolerated a single dose of 600 mg	62 (86.1%)	92 (89.3%)	27 (71.1%)	25 (96.2%)	17 (77.3%)	16 (76.2%)

peanut protein (response rate)						
(95% CI)	(75.9%, 93.1%)	(81.7%, 94.5%)	(54.1%, 84.6%)	(80.4%, 99.9%)	(54.6%, 92.2%)	(52.8%, 91.8%)
Subjects who tolerated a single dose of 1000 mg peanut protein (response rate)	52 (72.2%)	83 (80.6%)	22 (57.9%)	25 (96.2%)	15 (68.2%)	14 (66.7%)
(95% CI)	(60.4%, 82.1%)	(71.6%, 87.7%)	(40.8%, 73.7%)	(80.4%, 99.9%)	(45.1%, 86.1%)	(43.0%, 85.4%)
Subjects who tolerated a single dose of 2000 mg peanut protein (response rate)	37 (51.4%)	50 (48.5%)	14 (36.8%)	21 (80.8%)	10 (45.5%)	9 (42.9%)
(95% CI)	(39.3%, 63.3%)	(38.6%, 58.6%)	(21.8%, 54.0%)	(60.6%, 93.4%)	(24.4%, 67.8%)	(21.8%, 66.0%)

Results from the maintenance DBPCFC were used for group 1 subjects who did not complete the exit DBPCFC.
Confidence intervals were based on exact Clopper-Pearson intervals.

Maintenance with QD dosing was more effective than maintenance with nondaily dosing:

- Maintaining consistent QD dosing over a longer (56 weeks) versus a shorter period (28 weeks) reduced the maximum severity of symptoms upon exposure to any challenge dose of peanut protein at the exit DBPCFC, and consistent QD dosing was more effective at reducing the maximum severity of symptoms at any challenge dose of peanut protein than schedules that included nondaily QOD and BIW dosing.

Changes in peanut-specific immunoglobulins: Immunologic changes continued to improve over time.

- Treatment with Palforzia resulted in immunologic changes throughout the study consistent with published literature, as demonstrated by predicted changes in ps-IgE and IgG4, ps-IgE/IgG4 ratio, and peanut SPT mean wheal diameter.

Quality of life: Patient-reported outcomes indicated improved quality of life with longer-term treatment.

- Quality of life measured by subject- and parent-reported Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) exceeded the minimal clinically important differences in several domains related to disease-specific aspects.

ARC007 - Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES)

Phase 3, randomised, double-blind, placebo-controlled, multicentre study in North America evaluated the safety and tolerability of Palforzia in peanut-allergic subjects aged 4 to 17 years utilizing Palforzia.

No efficacy endpoints were evaluated. However immune parameters, (secondary endpoints) are documented below, as these may support treatment effects.

Design: The study consisted of a screening period and a double-blind treatment period that included initial dose escalation (2 days) and up-dosing (20-42 weeks), including at least 2 weeks of treatment at the maintenance dose of 300 mg/day.

Objectives:

Primary objective:

- To assess the safety and tolerability of AR101 for approximately 6 months in peanut-allergic children aged 4 to 17 years, inclusive

Secondary objectives:

- To measure the incidence of all treatment-related adverse events by study period, including adverse events of clinical interest
- To evaluate the effect of Palforzia on asthma control and immune parameters

Results:

Treatment with Palforzia resulted in immunologic changes throughout the study as demonstrated by changes in peanut IgE, IgG4, peanut IgE/IgG4 ratio, and mean peanut skin prick test wheal diameter consistent with previous studies.

The mean (SD) change in total IgE, peanut-specific IgE, and peanut-specific IgG4 from baseline to the end of up-dosing (300 mg visit) was higher in the AR101 group compared with the placebo group. The mean (SD) change in total IgE from baseline to the end of up-dosing (300 mg visit) was 389.4 (580.00) IU/mL for the AR101 group and -42.6 (328.11) IU/mL for the placebo group. The mean (SD) change in peanut-specific IgE from baseline to the end of up-dosing (300 mg visit) was 329.9 (506.30) kUA/L for the AR101 group and 60.3 (172.64) kUA/L for the placebo group. The mean (SD) change in peanut-specific IgG4 from baseline to the end of up-dosing (300 mg visit) was 6.347 (6.7742) mgA/L for the AR101 group and -0.149 (0.8602) mgA/L for the placebo group.

2.5.6. Discussion on clinical efficacy

The clinical development program for Palforzia was designed to demonstrated efficacy in the treatment of patients aged 4-17 years with a confirmed diagnosis of peanut allergy and for patients turning 18 years of age during treatment. The treatment should be used in conjunction with a peanut-avoidant diet. Palforzia is not intended for, and does not provide, immediate relief of allergic symptoms. Therefore, it is not to be used for emergency treatment of allergic reactions, including anaphylaxis.

Design and conduct of clinical studies

The Palforzia clinical development program in children, adolescents, and adults with peanut allergy included 2 phase 2 studies (ARC001, ARC002) and 7 phase 3 studies (ARC003, ARC004, ARC005, ARC007, ARC008, ARC010, ARC011). During the evaluation, study ARC004 (open-label follow-on ARC003 study) was completed and the final clinical study report was assessed during the procedure.

In all Palforzia clinical studies, efficacy was measured using a DBPCFC. This food challenge is a model for real world accidental exposure to food allergens and was performed according to the Practical Allergy (PRACTALL) guidelines with modification to include a 600 mg protein dose (between the 300 mg and 1000 mg challenge doses).

Dose-response studies

A "classical dose-finding" study was not performed for Palforzia within the development program. Selection and timing of each dose of peanut protein were based from literature data, as well as the work of the Consortium of Food Allergy Research (CoFAR).

Treatment with Palforzia is proposed to be administered in 3 sequential phases: Initial dose escalation, up-dosing, and maintenance. A dose level can be considered tolerated if no more than transient symptoms are observed with no or minimal medical intervention/therapy required.

Pivotal clinical studies (ARC003 and ARC010)

The efficacy of Palforzia was assessed in 2 randomised, double-blind, placebo-controlled, multicentre, phase 3 pivotal studies ARC003 (PALISADE) and ARC010 (ARTEMIS).

The first phase 3 pivotal study, ARC003, was conducted in both Europe and North America. In response to regulatory concerns that ARC003 did not enroll enough paediatric subjects from Europe to support the PIP, the applicant conducted ARC010, a second pivotal double-blind, placebo-controlled study in Europe only. The implementation of this "Europe-only" efficacy and safety phase 3 study was part of an EMA Scientific Advice, where differences in the study design between ARC003 and ARC010 were discussed (e.g. duration of maintenance or inclusion DBPCFC) and finally agreed.

Both studies consisted of screening and double-blind treatment periods that included initial dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (approximately 24-28 weeks for ARC003 and approximately 12-16 weeks for ARC010). In ARC010 study, the maintenance treatment was shorter than in ARC003 study.

A total of 671 randomised patients with peanut allergy contributed to the data efficacy analysis (ITT population ARC003 n=496; ARC010 n=175).

In ARC003, initially, patients being 4-55 years of age were eligible for inclusion. However hardly any adults were randomised (n=55) and 80% of subjects enrolled were aged 4 to 17 years. Although this "selection" of age group goes in line with the typical manifestation of peanut allergy in childhood, and likewise EAACI recommendations suggest treatment in children from around 4-5 years of age but depicted no recommendations for adults with peanut allergy (EAACI Guideline: AIT for IgE-mediated Food Allergy, 2017[34]), it is noted, that in opposite to the original, primary endpoint and key secondary efficacy evaluation, patients aged 18-55 years were subsequently excluded in ARC003 from the primary analyses set due to a protocol amendment.

In ARC010, subjects included were aged between 4-17 years which corresponds to the age window of the Palforzia indication.

For both studies, sample size and randomisation are considered acceptable. The overall SAP is agreed.

Both studies recruited subjects with a documented history of peanut allergy. Inclusion criteria addressed peanut-specific sensitisation parameters, like peanut-specific IgE level $\geq$ 0.35 kU/L and a SPT-wheal response $\geq$ 3 cm. The patients could concomitantly have other (food) allergies and asthma, which however should be stable. The eligibility criteria were adequate for the inclusion of patients with peanut allergy and comparable across the clinical studies with little modifications for study ARC010 pertaining to patients being slightly less sensitive to peanut protein. Additionally, a higher proportion of subjects in ARC003 had a history of systemic allergic reaction to peanut and a history of non-peanut food allergy compared with subjects in ARC010. Nevertheless, in general, most baseline characteristics were rather similar among the treatment groups across the phase 3 but also across performed phase 2 studies. The mean baseline values for assessments (including peanut-specific IgE, IgG4, skin prick test diameter, history of allergic diseases including asthma) were consistent with peanut allergy. The CHMP concluded that the inclusion criteria were adequate and representative of the patient population likely to seek treatment. Nevertheless, mainly Caucasians have been included in the Palforzia development programme despite some studies reporting that African American individuals as compared to Caucasian individuals are more likely to be sensitised to a broad range of allergens including peanuts, which cannot be explained by culture and exposure. In this context, the applicant will analyse the spontaneous adverse events reports by the reported race to look for

[34] Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799-815.

differences in character any severity of the events. The results of this analysis will be reported in the periodic safety updated reports (PSURs).

Subjects with a severe or life-threatening anaphylaxis event within 60 days of study entry and those with severe or uncontrolled asthma were excluded from the studies.

The screening DBPCFC for ARC003 was not to exceed 100 mg peanut protein (144 mg cumulative) leading to inclusion of more sensitive patients with peanut allergy than for ARC010, for which the screening DBPCFC was not to exceed 300 mg peanut protein (444 mg cumulative). The applicant stated that the enhancement to 300mg was chosen to allow subjects representative of the broader population with peanut allergy to enroll and because threshold levels for allergic reactions can vary day to day, the ARC010 screening DBPCFC criterion ensured that subjects with borderline sensitivity to 100 mg peanut protein were included..

The CHMP considered that the screening DBPCFC for ARC003 and ARC010 were acceptable.

The key measure of primary and secondary efficacy endpoints of Palforzia treatment, was the level of desensitization to peanut protein after a defined interval of study treatment, determined by the tolerated doses of peanut protein with no more than mild symptoms in a DBPCFC. In the pivotal studies ARC003 and ARC010, tolerability of a single dose of 1000 mg peanut protein (2043 mg cumulative; approximately 3-4 peanuts) with no more than mild symptoms at the exit DBPCFC was assessed as the primary efficacy endpoint. Additionally, the threshold sensitivity to peanut for an individual of challenge doses of 300 mg, 600 mg, and 1000 mg peanut protein were analysed. Other secondary endpoints included the maximum severity score and use of epinephrine during the exit DBPCFC and immunomodulatory markers such as peanut specific-IgE, IgG4, IgE-IgG4 ratio, and peanut specific skin prick test (SPT) wheal size. The DBPCFCs were conducted in accordance with the international recommended PRACTALL guidelines[35], with modifications to include a 600 mg dose (between 300 mg and 1000 mg). Choice of primary and key secondary endpoints, including standard efficacy variables being different in Europe and North America, are considered adequate by the CHMP and in line with the objectives of the studies.

The dosing regimen used in both phase 3 studies ARC003 and ARC010 was based on the regimen used in the phase 2 studies (please see also above 'Dose response studies'). Single-day initial dose escalation of Palforzia at low doses (0.5 mg up to 6 mg) was followed by up-dosing from 3 mg/day to the 300 mg/day dose with dose escalation every 2 weeks, and maintenance at 300 mg/day for approximately 3 months (ARC010) or 6 months (ARC003). The tolerability of single challenge doses of peanut protein or placebo from 3 mg to 1000 mg was evaluated in an exit DBPCFC to determine the level of peanut desensitisation reached by the subject. Patients should continue the standard peanut avoidance while participating in the study. Elaborate instructions concerning dose-modifications in case of intercurrent illness, presence of co-factors (e.g. exercise, menstruation, stress, fatigue, sleep deprivation or intake of nonsteroidal anti-inflammatory drugs or alcohol), and missed consecutive doses apply due to the risk of serious allergic reactions.

Efficacy data and additional analyses

Dose-finding studies

During the evaluation, CHMP questioned if differences in the timing schedule of Palforzia administration (including a more prolonged and slower up-dosing or a prolonged maintenance period), or a lower maintenance dose (< 300 mg) might have the same clinical effect but probably less side

[35] Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology PRACTALL consensus report. The journal of allergy and clinical immunology 130(6):1260-74

effects. The applicant responded that although a small study[33] suggested that slower up-dosing may lead to fewer adverse events leading to study discontinuation, while eventually reaching desensitisation, the study was small and there are no robust evidence of efficacy and safety for a slower up-dosing and lower maintenance doses. The applicant also said that the option of a lower maintenance dose was not considered because no Palforzia phase 2 data or published data were available to support reaching clinically relevant levels of desensitisation at daily maintenance doses of less than 300 mg or equivalent protein content of approximately 1 peanut kernel. With regard to a non-daily maintenance dosing schedule, the applicant referred to the completed follow-on study ARC004 which suggests that non-daily maintenance dosing appears not to be as effective as daily dosing in maintaining clinically relevant efficacy. In addition, a lower incidence of treatment-related adverse events was reported with daily maintenance dosing compared with non-daily dosing regimens. As a consequence, the importance of daily dosing is added in section 4.2 the SmPC and it is highlighted that treatment interruption can potentially lead to increased adverse events. Furthermore, appropriate dose modification instructions are included in the product information allowing the physician to temporary modify the dose of Palforzia for patients who experience allergic reactions during up-dosing or maintenance or for practical reasons for patient management.

CHMP agreed with the approach taken (see also 'Dose response studies' section 2.5.1.).

Efficacy data from pivotal studies and additional analyses

The primary efficacy endpoint (percentage of patients tolerating a single dose of 1000 mg peanut protein in DBPCFC at study end) was met in studies ARC003 and ARC010. Treatment with Palforzia in the ITT population (4-17 years) resulted in statistically significant treatment effects over placebo, with treatment differences of 47.8% ($p < 0.0001$) in ARC003 and 56.0% ($p < 0.0001$) in ARC010. In the completer population of subjects aged 4 to 17 years, the proportion of subjects who tolerated a single dose of 1000 mg peanut protein at the exit DBPCFC with no more than mild symptoms was 63.2% for Palforzia-treated subjects in ARC003 and 72.6% in ARC010.

Significant treatment effects of Palforzia compared with placebo were also observed for key secondary endpoints of desensitisation response and maximum severity of symptoms for subjects aged 4 to 17 years. In addition, further supportive and sensitivity subgroup analyses as well as sensitivity analyses using predefined analysis populations and worst-case imputation methods supported the results. The proportion of subjects in the completer population who tolerated a single dose of 600 mg and 300 mg peanut protein with no more than mild symptoms were 84.5% and 96.3%, respectively in ARC003, and 84.9% and 91.5%, respectively, in ARC010. Nevertheless, it was noted that a considerable number of patients (20-35% in ARC010) could not tolerate a single dose of 300 mg peanut protein (although on maintenance) and continuing treatment in this subgroup of patients may not be reasonable. 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. Treatment must be discontinued if symptoms requiring medical intervention (e.g., use of adrenaline) occur with any dose during initial dose escalation. Allergic reactions, including gastrointestinal reactions, that are severe, recurrent, bothersome, or last longer than 90 minutes during up-dosing or maintenance should be actively managed with dose modifications. Clinical judgment should be used to determine the best course of action on a patient by patient basis. This is adequately reflected in section 4.2 of the SmPC.

In addition, the maximum severity of symptoms at any challenge dose during the exit DBPCFC for subjects aged 4 to 17 years in the ITT populations of ARC003 and ARC010 was reduced in the Palforzia group compared with placebo. In ARC003, the maximum severity of symptoms among treated subjects was no symptoms (37.6% Palforzia, 2.4% placebo), mild symptoms (32.0%, 28.2%), moderate symptoms (25.3%, 58.9%), and severe symptoms (5.1%, 10.5%). In ARC010, the maximum severity

of symptoms was no symptoms (35.6% Palforzia, 0% placebo), mild symptoms (41.7%, 37.2%), moderate symptoms (18.2%, 46.5%), and severe symptoms (4.5%, 16.3%).

At the request of CHMP, additional paediatric subgroups analyses in the ITT population were performed by geographic region (Europe, North America), by age group (4-11 years, 12-17 years), and by region and age group (Europe 4-11 years, 12-17 years; North America 4-11 years, 12-17 years) for the primary efficacy endpoint for ARC003 and ARC010 studies.

For ARC003, all performed supportive analyses to the primary efficacy endpoint were consistent with the overall ITT results, except the supportive analysis for the Europe region in the 12 to 17 years age group, which was not statistically significant (tolerated 1000 mg peanut protein: 55.6% Palforzia, 33.3% placebo; treatment difference, 22.2% [95% CI: -37.3, 81.7]; p = 0.4642). This could be explained due to low numbers of participants in the EU region (27 vs 3).

For ARC010, treatment differences (Palforzia-placebo) were consistent with the primary efficacy endpoint for the regional populations by country in countries that enrolled a sufficient number of subjects. Subgroup analyses by age group (4-11 years, 12-17 years) for the primary efficacy endpoint were also consistent with the overall ITT results; however, the treatment difference was less, but still statistically significant for the smaller age group of 12 to 17 years. Among patients aged 4-11 years, 52-60% tolerated 1000 mg peanut protein, while 45-46% patients aged 12-17 years and 34% of patients aged 18-55 years met this endpoint at the exit DBPCFC.

In order to further characterise the populations, who might profit most, the applicant was asked to provide further efficacy data comparing highly allergic individuals with less allergic patients by subdividing patients by degree of severity in peanut-allergic individuals in several subgroups including specific sensitisation levels and baseline food challenge results, as well as age and patients history. Performed analysis according to age revealed that both studies showed robust efficacy data for included subjects aged 4-17 years. From these, a higher response rates in younger children, aged 4-11 years (52.5% in ARC003 and 62.9% in ARC010) versus older children, aged 12-17 years (46.3% in ARC003 and 45.7% in ARC010) was observed. Interestingly, the highest response rate (62.9%) was reached in children aged 4-11 years in the European only study ARC010, although their treatment maintenance phase was half as long as in ARC003. This may be associated with slightly different inclusion criteria (leading to "some less sensitive subjects" being included), but it may also support the impact of "age", as included children were slightly younger in ARC010 (median 8 years). By performing the descriptive sub analyses according to subgroups as defined by IgE, SPT, and DBPCFC, younger, less sensitive subjects, seem to develop the best efficacy rates. However, these descriptive post-hoc sub analysis can only be considered exploratory, as the studies were not designed to investigate such subgroups. In addition, especially in the age group of 12-17 years, sample sizes are too small to enable persistent conclusions.

Key secondary efficacy endpoints were met in hierarchical order for the ITT population (subjects aged 4-17 years) in ARC003 and in ARC010, thus key secondary endpoint in study ARC003 for subjects aged 18 to 55 years was not met.
A subgroup analysis in patients who turned age 18 years during Palforzia treatment was also performed as the proposed indication recommends that Palforzia may be continued in patients 18 years of age and older. As the initially submitted data in this subgroup was small, the applicant provided an updated data set and reported 51 patients which were enrolled at age ≤ 17 years and subsequently turned age 18 during treatment with Palforzia (enrolled in different studies: ARC003, ARC010, ARC0101 respectively in follow-on studies ARC004 and ARC008). From these 51 patients nearly two-thirds of the subjects who turned age 18 during Palforzia treatment (33 subjects, 64.7%) remain ongoing in the follow-on study ARC008. The response rate of Palforzia treated subjects who turned 18 years whilst participating in a study and tolerated a single highest dose of at least 1,000 mg

peanut protein with no more than mild allergic symptoms at the exit DBPCFC (15/27, 55.6%) was consistent with the overall primary efficacy of the subjects aged 4 to 17 years.
CHMP noted the results and agreed that Palforzia may be continued in patients 18 years of age and older.

The analysis of other secondary efficacy endpoints documented that treatment with Palforzia decreased the need for epinephrine use as rescue medication during the peanut challenge at the exit DBPCFC compared with the screening DBPCFC. For subjects aged 4 to 17 years who completed the peanut challenge day of the exit DBPCFC (completer population), no subject in either treatment group used epinephrine as rescue medication during the placebo challenge day of the screening DBPCFC and a similar proportion of subjects in each treatment group (ARC003: 36.1% AR101, 37.1% placebo; ARC010: 20.8% AR101, 20.0% placebo) used epinephrine as rescue medication during the peanut challenge day. The higher proportion of subjects with epinephrine use during the screening DBPCFC in ARC003 compared with ARC010 may be due to different rates of epinephrine use in Europe compared with North America. During the peanut challenge day of the exit DBPCFC, epinephrine was used as rescue medication in 9.5% of Palforzia-treated subjects and 53.4% of placebo-treated subjects in ARC003, and 2.8% of Palforzia-treated subjects and 17.5% of placebo-treated subjects in ARC010.

Overall, CHMP considered that the presented data are endorsed, statistically significant, and consistent.

With regard to duration of treatment, the applicant presented first data which indicates, that a prolonged maintenance treatment with Palforzia seems to maintain or even further increase efficacy, determined by DBPCFC (with a data set of n=104 subjects). Participants (originated from ARC003 enrolled in the follow-on study ARC004) were treated for in total approximately 18 months (580.5 days; range, 388-761 days). From these 104 subjects, 83 (79.8%) tolerated at least 1000 mg peanut protein (2043 mg cumulative) at the ARC004 exit DBPCFC. The data is supported by immunological data including a further decrease of specific IgE and increase of specific IgG4 as well as decrease in Mean (SD) skin prick test mean wheal diameter. Meanwhile efficacy data from the follow-on study ARC004 that extended the maintenance period of the ARC003 showed that efficacy were maintained or improved in a large proportion of subjects. Patients have been followed for a maximum of two years (n=26) by the latest cut-off date: after 18 months maintenance, n=21 from 26 subjects tolerated 2000 mg at exit DBPCFC, and n= 25% tolerated 1000 mg peanut protein at the Exit DBPCFC.

CHMP noted that in group 1 (former placebo treated subjects), only 55 of 102 subjects (53.9%) completed the study. The applicant further confirmed this observation and argued that the long treatment phase may be responsible for high discontinuation rate. CHMP accepted this explanation.

Current clinical data (2 years) for ongoing treatment with Palforzia is regarded as consistent with demonstration of a "sustained clinical effect" as described in the CHMP guideline "Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases" (CHMP/EWP/18504/06). The SmPC has been updated to include that efficacy data are currently available for up to 24 months of treatment with Palforzia and no recommendation can be made about the duration of treatment beyond 24 months. This is adequately reflected in the SmPC. The effect of stopping treatment on maintenance of clinical efficacy or the effect on a potential disease modification has not been evaluated. This is adequately reflected in the SmPC and it is recommended that if treatment with Palforzia is stopped, patients must continue to carry self-injectable adrenaline at all times. Furthermore, treatment with Palforzia should be used in conjunction with a peanut-avoidant diet. In addition the applicant will collect further data to support sustained clinical effect and long-term efficacy (potential disease modification) within the open-label extension study ARC008 listed in the RMP. With this, the applicant follows the recommendation of the CHMP to propose a protocol to ensure

the collection of sufficient data to clarify the long-term efficacy and safety in Palforzia treated patients, who end treatment with Palforzia after 5 years or earlier. The applicant has clarified how discontinuation rates, immunological markers and long-term efficacy will be assessed in study ARC008, which will be extended to 5 years treatment + 12 month follow-up.

Regarding quality of life, in study ARC003 treatment with Palforzia resulted in similar values at exit as baseline measured by subject and parent reported FAQLQ and FAIM. This result reflects other literature data on this topic. A meaningful change in QoL aspects needs more time than the study duration of ARC003 to be adequately assessed. Indeed, many subjects experienced an improvement in tolerated amount of peanut protein; however, they were still blinded and did not "experience" real life situations. In the follow-up study ARC004, patient-reported outcomes indicated improved quality of life with longer-term treatment. Quality of life measured by subject and FAQLQ and FAIM exceeded the minimal clinically important differences in several domains related to disease-specific aspects.

With regard to compliance, there was a clear age effect in treatment compliance (PP population) with 85% completers in the 4-11 year age group, 69% completers in the 12-17 year age group, and 48% of (the relatively few) patients aged 18-55 years (ARC003) completing the studies. It is acknowledged that with a complex dosing regimen and potential for significant adverse events patient compliance, in particular in adolescents, may not be 100%. Careful selection and appropriate education of adolescent patients will be required to ensure compliance with the treatment and the necessary precautions. The section 4.2 of the SmPC highlight the importance of a daily maintenance treatment to maintain the tolerability and clinical effects of Palforzia. In addition, healthcare professional and patient/caregiver educational materials and a patient card have been put in place to provide education and counselling regarding the appropriate use, adverse reactions and their management, and when to seek medical care (see also clinical safety discussion 2.6.1.).

CHMP agreed that treatment with Palforzia requires an active participation and a shared-decision making between patients (and families) and the treating physician and may not be suitable for all patients allergic to peanut.

2.5.7. Conclusions on the clinical efficacy

The design and conduct of the 2 phase 3 clinical studies (ARC003 and ARC010) as well as the number of patients with peanut allergy included in the clinical program (496 in ARC003 and 175 in ARC010) is considered adequate for the analysis of clinical efficacy.

The 2 phase 3 studies met their primary and key secondary endpoint, i.e. significantly higher number of patients in the Palforzia groups, who tolerated 1000 mg, 600 mg, and 300 mg peanut protein at the exit DBPCFC, as compared to the placebo groups. These outcomes were confirmed by supportive subgroup as well as sensitivity analyses.

Overall, a favorable treatment effect in the indicated age group of 4-17 years of age has been shown by several endpoints, statistically robust and clinically relevant. Patients who keep up the treatment up to and throughout the maintenance phase showed a very convincing increase in their individual threshold of reactivity against peanut protein. Therefore, patients treated with Palforzia may continue the treatment when they become 18 years of age and older. The limited data on quality of life substantiate that this effect is clinically relevant and may reduce stress and anxiety connected with peanut allergy. Efficacy data are currently available for up to 24 months of treatment with Palforzia and no recommendation can be made about the duration of treatment beyond 24 months. The effect of stopping treatment on maintenance of clinical efficacy or on disease modification has not been evaluated and further data on sustained clinical effect will be collected in the study ARC008.

In conclusion, the CHMP considered that the data submitted support the following indication:

"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."

2.6. Clinical safety

The safety profile of Palforzia in patients with peanut allergy is derived from 5 clinical studies involving 944 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 ongoing, uncontrolled, follow-on studies, ARC004 and ARC011 (data cut-off date 15 Dec 2018)

Patient exposure

Controlled Population:

In the combined controlled population, 841 subjects were treated with Palforzia and 335 subjects were treated with placebo from the 3 controlled studies (ARC003, ARC007, ARC010).

During initial dose escalation, subjects in both treatment groups were treated for a median of 2.0 days. During up-dosing, 818 subjects in the Palforzia group were treated for a median of 154.0 days (22 weeks) and 332 subjects in the placebo group were treated for a median of 149.0 days. The maintenance dose of 300 mg/day was reached by 83.4% of subjects in the Palforzia group and 95.5% of subjects in the placebo group.

In study ARC010 at 300 mg/day, 108 subjects in the Palforzia group were treated for a median of 103.5 days (approximately 15 weeks).

In study ARC003 at 300 mg/day, 310 subjects in the Palforzia group were treated for a median of 175.0 days (25 weeks).

Table 10 Extent of Exposure: Palforzia (AR101) or Placebo at 300 mg/day in ARC010 and ARC003 (Controlled Population)

	ARC010 300 mg/day		ARC003 300 mg/day	
	AR101 (N =108)	**Placebo (N =41)**	**AR101 (N = 310)**	**Placebo (N = 118)**
Duration of exposure (days) [1]				
Mean (SD)	125.0 (50.87)	112.7 (38.98)	176.2 (25.33)	178.1 (17.15)
Median	103.5	97.0	175.0	175.5
Q1, Q3	91.0, 128.5	90.0, 125.0	172.0, 183.0	173.0, 182.0
Min, max	69, 265	18, 217	15, 292	58, 250
Max dose reached by category (mg/day)				
240	0	0	1 (0.3%)	0
300	108 (100%)	41 (100%)	309 (99.7%)	118 (100%)

[1] Duration of exposure to study treatment was calculated as the date of last dose of study product minus the date of first dose of study product plus 1.

min, minimum; max, maximum; Q1, Q3, first quartile, third quartile.

Integrated Safety Population:

In the integrated safety population, 944 subjects were treated with Palforzia that make up the population of all treated subjects from the 5 studies (ARC003, ARC007, ARC010, ARC004, ARC011).

Among the 944 unique individuals exposed to Palforzia, 770 patients were exposed to the target dose of Palforzia 300 mg/day for a mean of approximately nine months (310 patients were exposed for a mean of approximately six months to Palforzia during the controlled study phase). The exposure is summarised in Table 11.

Table 11 Extent of exposure (Integrated Safety Population)

	IDE (N = 944)	**Up-Dosing (N = 919)**	**300 mg/day (any weeks) (N = 770)**	**Overall (any dose) (N = 944)**
Duration of exposure (days) [1]				
Mean (SD)	2.0 (0.16)	153.9 (46.37)	244.8 (138.77)	351.8 (182.54)
Median	2.0	154.0	189.0	342.0
Q1, Q3	2.0, 2.0	141.0, 173.0	172.0, 366.0	249.5, 470.5
Min, max	1, 2	1, 434	1, 629	1, 842
Max dose reached (mg/day)				
Mean (SD)	11.8 (1.29)	263.6 (96.12)	299.9 (2.16)	257.2 (102.41)
Median	12.0	300.0	300.0	300.0
Q1, Q3	12.0, 12.0	300.0, 300.0	300.0, 300.0	300.0, 300.0
Min, max	3, 12	3, 1200	240, 300	3, 1200

[1] Duration of exposure to study treatment was calculated as the date of last dose of study product minus the date of first dose of study product plus 1.

Demographics

The included patient population was representative of the peanut allergic population. The demographics were balanced between the Palforzia and placebo groups. The majority of patients were aged between 4 and 17 years of age, which is the target population. Generally, more boys are included in peanut OIT studies in the literature; this is also noted for the Palforzia programme.

Table 12 Demographics and Baseline Characteristics (Safety population)

	Controlled		**Integrated [1]**
Characteristic	**AR101 (N = 841)**	**Placebo (N = 335)**	**AR101 (N = 944)**
Age [2]			
Median	9.0	9.0	9.0
Min, max	4, 17	4, 17	4, 19
Age category			
4-11 Years	561 (66.7%)	233 (69.6%)	630 (66.7%)
12-17 Years	280 (33.3%)	102 (30.4%)	311 (32.9%)
≥ 18 Years [3]	0	0	3 (0.3%)
Sex			
Male	494 (58.7%)	205 (61.2%)	561 (59.4%)

Characteristic	Controlled		Integrated [1]
	AR101 (N = 841)	Placebo (N = 335)	AR101 (N = 944)
Female	347 (41.3%)	130 (38.8%)	383 (40.6%)
Race			
White	643 (76.5%)	244 (72.8%)	723 (76.6%)
Not white	187 (22.2%)	87 (26.0%)	210 (22.2%)
Total IgE (kU/L)			
n	758	298	861
Median	466.00	469.00	475.00
Q1, Q3	227.00, 903.00	254.00, 1040.00	231.00, 937.00
Min, max	8.0, 7674.0	58.0, 4545.0	8.0, 8190.0
Peanut-specific IgE (kUA/L) [4]			
n	835	333	938
Median	81.40	75.00	83.85
Q1, Q3	29.40, 200.00	34.00, 176.50	30.00, 208.00
Min, max	0.1, 2735.0	0.4, 1912.0	0.1, 2735.0
Skin prick test mean wheal diameter (mm) [4, 5]			
n	835	333	936
Median	11.50	12.50	11.50
Q1, Q3	9.00, 16.00	9.50, 16.00	9.00, 15.50
Min, max	0.0, 52.5	2.0, 40.0	0.0, 52.5
Childbearing potential			
n	347	130	383
Yes	91 (26.2%)	42 (32.3%)	105 (27.4%)
No - premenarche	255 (73.5%)	88 (67.7%)	276 (72.1%)
No - other	1 (0.3%)	0	2 (0.5%)

[1] For subjects treated with AR101 in the originating study, data are from the originating study. For subjects treated with placebo in the originating study, data are from the follow-on study with AR101. Includes all randomised subjects who received at least 1 dose of study product.

[2] Calculated relative to the date of informed consent.

[3] Three subjects in the 12 to 17 years category received placebo in ARC003 and turned age 18 years before enrollment in ARC004 group 1.

[4] Inclusion criteria required meeting a threshold for peanut-specific IgE and/or skin prick test; thus, minimum values in the range of values could be below the threshold requirement for either test.

[5] Calculated as the average of the long and short axis from the peanut wheal minus the average of the long and short axis from the saline wheal.

Ig, immunoglobulin; min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

Adverse events

Treatment-emergent Adverse Events:

The treatment emergent adverse events (TEAEs) are presented in Table 13 for the integrated safety population and in Table 14 for the controlled population. The TEAEs for the integrated safety population were comparable to the controlled population.

Table 13 Overall Summary of Treatment-Emergent Adverse Events (Integrated Safety Population)

	IDE (N = 944)	Up-Dosing (N = 919)	300 mg/day (any weeks) (N = 770)	Overall (any dose) (N = 944)
Subjects with at least 1 adverse event	481 (51.0%)	891 (97.0%)	687 (89.2%)	933 (98.8%)
By severity				
Grade 1: Mild	426 (45.1%)	438 (47.7%)	446 (57.9%)	373 (39.5%)
Grade 2: Moderate	54 (5.7%)	430 (46.8%)	226 (29.4%)	522 (55.3%)
Grade 3: Severe	1 (0.1%)	22 (2.4%)	15 (1.9%)	37 (3.9%)
Grade 4: Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Grade 5: Death	0	0	0	0
Related to study product	426 (45.1%)	788 (85.7%)	444 (57.7%)	851 (90.1%)
Led to study product discontinuation	20 (2.1%)	80 (8.7%)	9 (1.2%)	108 (11.4%)
Systemic allergic reaction	6 (0.6%)	80 (8.7%)	76 (9.9%)	143 (15.1%)
Associated with non-study product food allergen exposure	3 (0.3%)	110 (12.0%)	82 (10.6%)	174 (18.4%)
Serious adverse event	0	7 (0.8%)	8 (1.0%)	14 (1.5%)
By severity				
Grade 1: Mild	0	2 (0.2%)	0	1 (0.1%)
Grade 2: Moderate	0	3 (0.3%)	4 (0.5%)	7 (0.7%)
Grade 3: Severe	0	1 (0.1%)	4 (0.5%)	5 (0.5%)
Grade 4: Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Grade 5: Death	0	0	0	0
Related to study product	0	3 (0.3%)	2 (0.3%)	5 (0.5%)
Total no. exposure-years	5.10	387.13	516.14	909.12
Total no. adverse events (exposure-adj)	1358 (266.1)	29514 (76.2)	11636 (22.5)	42508 (46.8)

Adj, adjusted; IDE, initial dose escalation.

Table 14 Overall Summary of Treatment-Emergent Adverse Events (Controlled Population)

	Combined IDE and Up-Dosing		ARC010 300 mg/day		ARC003 300 mg/day	
	AR101 (N = 841)	Placebo (N = 335)	AR101 (N = 108)	Placebo (N = 41)	AR101 (N = 310)	Placebo (N = 118)
Subjects with at least 1 adverse event	823 (97.9%)	311 (92.8%)	95 (88.0%)	32 (78.0%)	270 (87.1%)	94 (79.7%)
By severity						
Grade 1: Mild	399 (47.4%)	205 (61.2%)	77 (71.3%)	28 (68.3%)	161 (51.9%)	57 (48.3%)
Grade 2: Moderate	402 (47.8%)	101 (30.1%)	18 (16.7%)	4 (9.8%)	101 (32.6%)	37 (31.4%)
Grade 3: Severe	21 (2.5%)	4 (1.2%)	0	0	8 (2.6%)	0
Grade 4: Life-threatening	1 (0.1%)	0	0	0	0	0
Grade 5: Death	0	1 (0.3%)	0	0	0	0
Related to study product	745 (88.6%)	190 (56.7%)	57 (52.8%)	5 (12.2%)	159 (51.3%)	26 (22.0%)
Led to study product discontinuation	92 (10.9%)	8 (2.4%)	0	0	4 (1.3%)	0

Systemic allergic reaction	77 (9.2%)	11 (3.3%)	8 (7.4%)	1 (2.4%)	27 (8.7%)	2 (1.7%)
Associated with non-study product food allergen exposure	96 (11.4%)	64 (19.1%)	5 (4.6%)	4 (9.8%)	28 (9.0%)	24 (20.3%)
Serious adverse event	7 (0.8%)	4 (1.2%)	0	0	4 (1.3%)	1 (0.8%)
By severity						
Grade 1: Mild	2 (0.2%)	1 (0.3%)	0	0	0	1 (0.8%)
Grade 2: Moderate	3 (0.4%)	1 (0.3%)	0	0	2 (0.6%)	0
Grade 3: Severe	1 (0.1%)	1 (0.3%)	0	0	2 (0.6%)	0
Grade 4: Life-threatening	1 (0.1%)	0	0	0	0	0
Grade 5: Death	0	1 (0.3%)	0	0	0	0
Related to study product	3 (0.4%)	0	0	0	1 (0.3%)	0
Total no. exposure-years	347.15	138.65	36.95	12.65	149.54	57.55
Total no. adverse events (exposure-adjusted)	28359 (81.7)	4022 (29.0)	1368 (37.0)	178 (14.1)	4041 (27.0)	650 (11.3)

During up-dosing the incidence of AEs of any severity was more pronounced compared to initial dose escalation and daily dosing.

Interestingly, placebo treated patients complained in comparable amounts of TEAEs (including severity of AEs), than Palforzia treated subjects (ARC003; Controlled Population, Table 14: 48% of placebo subjects complained about mild reactions, 31% about moderate reactions; Palforzia group: 52% mild and 33% moderate AEs). In the Palforzia group 51.3% AEs were related to the study product, but only 22.6% of AEs in the placebo group. AEs related to study products were announced in 56.7% (placebo) and 88.6% (Palforzia) during IDE and up-dosing.

In the integrated safety population overall 11.4% of subjects had 1 or more AEs that led to study product discontinuation. This was higher during up-dosing (8.7%) than initial dose escalation (2.1%) and all 300 mg/day dosing (1.2%).

In the controlled population 10.9% Palforzia and 2.4% placebo group subjects had one or more AEs leading to study product discontinuation during initial dose escalation and up-dosing combined. In the Palforzia group, 4 subjects (1.3%) discontinued study product due to 1 or more adverse events during 300 mg/day dosing in ARC003 and 0 in ARC010. In the placebo group, no subject discontinued study product due to 1 or more adverse events during 300 mg/day dosing in ARC003 or ARC010.

Treatment-Related Adverse Events:

With regard to common adverse events, both safety populations (controlled and integrated) showed a comparable adverse event profile. In the controlled population, the most common adverse events (≥20% of subjects) during initial dose escalation and up-dosing combined with incidence at least 5% higher over the placebo group in decreasing order were abdominal pain, throat irritation, pruritus, vomiting, nausea, cough, urticaria, upper abdominal pain, oral pruritus, abdominal discomfort, and sneezing. In the integrated safety population, the most common adverse events (≥20% of subjects) during up-dosing were abdominal pain, throat irritation, vomiting, cough, nausea, pruritus, urticaria, upper abdominal pain, oral pruritis, headache, abdominal discomfort, rhinorrhea, sneezing, and upper respiratory tract infection. During 300 mg/day maintenance treatment in the integrated safety population, cough and urticaria were the only events that reached at least 20% incidence, and urticaria was the only event to reach 20% incidence in Palforzia-treated subjects during maintenance in the ARC010 and ARC003 controlled populations (abdominal pain and pruritus were > 20% in ARC010).

Abdominal pain was described in the highest rates during up-dosing Palforzia 415 (49.3%), Placebo 59 (17.6%). Although reducing to 3.4% - 9% during maintenance, (Table 15, abdominal pain is still

present. Especially while focusing on eosinophilic gastrointestinal diseases, this should be further reviewed in the post-authorisation safety study ARC008 (safety discussion in 2.6.1.).

Adverse events over time:

There seemed to be a decrease in the proportions of subjects with the most common adverse events over time from the first 0 to 13 weeks to > 52 weeks of 300 mg/day dosing. The proportions of subjects with any adverse event decreased over time during 300 mg/day dosing from 76.4% for 0 to 13 weeks to 50.8% for > 52 weeks (Table 19). The amount of "subjects with at least 1 AE related to study product" even decreased from 46.9% for 0 to 13 weeks to 19.3% for > 52 weeks. However anaphylactic reactions (as a Treatment-related AE) occurred in 3 – 4.3% rather constantly during 300 mg/day dosing – rather independently from time (Table 15).

Table 15 Treatment-Related Adverse Events in ≥ 10% of Subjects Overall During 300 mg/day Dosing by Interval and Preferred Term (Integrated Safety Population)

Preferred Term	300 mg/day (N = 770)	300 mg/day (N = 700)	300 mg/day (N = 449)	300 mg/day (N = 197)
Subjects with at least 1 adverse event related to study product	361 (46.9%)	233 (33.3%)	111 (24.7%)	38 (19.3%)
Abdominal pain	72 (9.4%)	42 (6.0%)	18 (4.0%)	6 (3.0%)
Throat irritation	86 (11.2%)	47 (6.7%)	19 (4.2%)	8 (4.1%)
Pruritus	62 (8.1%)	43 (6.1%)	4 (0.9%)	2 (1.0%)
Nausea	54 (7.0%)	24 (3.4%)	7 (1.6%)	5 (2.5%)
Vomiting	43 (5.6%)	23 (3.3%)	11 (2.4%)	7 (3.6%)
Urticaria	74 (9.6%)	46 (6.6%)	16 (3.6%)	6 (3.0%)
Oral pruritus	46 (6.0%)	26 (3.7%)	11 (2.4%)	5 (2.5%)
Abdominal discomfort	39 (5.1%)	17 (2.4%)	5 (1.1%)	1 (0.5%)
Abdominal pain upper	38 (4.9%)	21 (3.0%)	13 (2.9%)	4 (2.0%)
Cough	32 (4.2%)	25 (3.6%)	11 (2.4%)	4 (2.0%)
Sneezing	22 (2.9%)	10 (1.4%)	5 (1.1%)	2 (1.0%)
Paraesthesia oral	43 (5.6%)	16 (2.3%)	7 (1.6%)	1 (0.5%)
Throat tightness	22 (2.9%)	3 (0.4%)	2 (0.4%)	0
Anaphylactic reaction	33 (4.3%)	24 (3.4%)	15 (3.3%)	6 (3.0%)
Rhinorrhoea	17 (2.2%)	9 (1.3%)	3 (0.7%)	1 (0.5%)
Rash	19 (2.5%)	13 (1.9%)	6 (1.3%)	1 (0.5%)
Nasal congestion	13 (1.7%)	6 (0.9%)	5 (1.1%)	2 (1.0%)
Lip pruritus	25 (3.2%)	12 (1.7%)	10 (2.2%)	1 (0.5%)

Summary includes all adverse events with at least 5% incidence overall.

The anaphylactic reaction preferred term includes systemic allergic reactions of any severity, including anaphylaxis (severe).

To further follow the assumption of the applicant, that the number of allergic reactions over time decrease, a requested presentation of a tabular comparison with the number of systemic allergic reactions per year and per year during lifetime before study start is presented for ARC003 (Table 16). Considering limitations like pre-study estimates are based on self-reported history baseline data in ARC003 show comparable rates. But rates increased after treatment – indicating an enhancement of allergic reactions induced by treatment (and not by accidental reactions, co-factors or others, as the rate in the placebo group is lower). Another analysis (please see Section Serious Adverse Events) documents, that the incidence of systemic allergic reactions did not appear to decrease over the course

of the individual studies, neither did the severity of the systemic allergic reactions appear to change over the treatment course.

Table 16 Summary of Systemic Allergic Reactions per Year Before and After Start of Study in ARC003 (Safety Population, 4-17 Years)

	AR101 (N = 372)	Placebo (N = 124)
No. systemic allergic reactions per year during lifetime prior to start of therapy (self-reported history)		
Mean (SD)	0.15 (0.187)	0.15 (0.201)
Median	0.11	0.11
Q1, Q3	0.00, 0.20	0.00, 0.19
Min, max	0.0, 2.0	0.0, 1.2
No. systemic allergic reactions per year while on study		
Mean (SD)	1.29 (18.950)	0.03 (0.191)
Median	0.00	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00
Min, max	0.0, 365.3	0.0, 1.2

Min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

Eosinophilic gastrointestinal disorders:

Eosinophilic esophagitis (EoE) was diagnosed in 5 of 944 subjects (0.5% overall) in the controlled and integrated safety populations. 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.

Outside of the integrated safety population, 7 additional subjects had a diagnosis of EoE: 2 subjects in the phase 2 studies ARC001 and ARC002, 1 adult subject in study ARC004, and 4 subjects in study ARC008 (3 subjects with grade 2 moderate and one subject with severity unknown).

Table 17 Summary of Subjects With EoE (Integrated Safety Population, 4-17 Years)

Study	Nb subjects	Age	Serious	Period, Study Day	AR101 Dose	Severity, Relationship
ARC003	1	10	No	Up-dosing, 176	200 mg	Mild, related
ARC004	2	13	No	Up-dosing, 50	12 mg	Severe, not related
ARC004	2	9	No	300 mg/day, 293	300 mg	Moderate, related
ARC007	1	17	No	Up-dosing, 79	80 mg	Mild, not related
ARC007	1	9	No	Up-dosing, 138	40 mg	Moderate, related

According to the data, no placebo treated subjects developed EoE. Only one subject in the placebo group discontinued study due to chronic/recurrent GI AEs, versus n=38 of AR101 treated subjects.

Serious adverse event/deaths/other significant events

Deaths

One death due to a traffic accident was recorded for a patient in the placebo group. No other death occurred.

Serious adverse events

It appears that not all cases of e.g. anaphylaxis or EoE were reported/summarised as related serious adverse events. The related adverse events as judged by the applicant (although without a justification) are shown in the Table 18 and comprised, among others, four cases of anaphylaxis and one case of asthma.

Table 18 Treatment-Emergent and Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Integrated Safety Population)

System Organ Class Preferred Term	Up-Dosing (N = 919)	300 mg/day (any weeks) (N = 770)	Overall (any dose) (N = 944)
Subjects with at least 1 serious adverse event	7 (0.8%)	8 (1.0%)	14 (1.5%)
Immune system disorders	2 (0.2%)	2 (0.3%)	4 (0.4%)
Anaphylactic reaction	2 (0.2%)	2 (0.3%)	4 (0.4%)
Infections and infestations	1 (0.1%)	3 (0.4%)	4 (0.4%)
Gastroenteritis	0	1 (0.1%)	1 (0.1%)
Gastroenteritis viral	0	1 (0.1%)	1 (0.1%)
Pharyngitis streptococcal	0	1 (0.1%)	1 (0.1%)
Pneumonia mycoplasmal	1 (0.1%)	0	1 (0.1%)
Streptococcal infection	0	1 (0.1%)	1 (0.1%)
Injury, poisoning, and procedural complications	1 (0.1%)	2 (0.3%)	3 (0.3%)
Concussion	0	1 (0.1%)	1 (0.1%)
Humerus fracture	0	1 (0.1%)	1 (0.1%)
Intentional overdose	1 (0.1%)	0	1 (0.1%)
Respiratory, thoracic, and mediastinal disorders	2 (0.2%)	0	2 (0.2%)
Asthma	2 (0.2%) [1]	0	2 (0.2%)
Gastrointestinal disorders	0	1 (0.1%)	1 (0.1%)
Abdominal pain	0	1 (0.1%)	1 (0.1%)
Metabolism and nutrition disorders	0	1 (0.1%)	1 (0.1%)
Dehydration	0	1 (0.1%)	1 (0.1%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.1%)	0	1 (0.1%)
Acute lymphocytic leukaemia	1 (0.1%)	0	1 (0.1%)

The anaphylactic reaction preferred term includes systemic allergic reactions of any severity, including anaphylaxis (severe).

Shading indicates subjects with events that were considered treatment related (not carried to overall column).

No subject had a serious adverse event during initial dose escalation.

[1] Only 1 subject's asthma was considered treatment related.

Additionally, when focusing on AEs Grade ≥ 3 severity, hardly any placebo reactions occurred. In n=818 Palforzia treated subjects, gastrointestinal disorders had been reported the most (1.1%). In this analysis of the controlled population, AEs occurred especially during up-dosing and not during maintenance therapy.

Furthermore, in the integrated safety population, (AEs Grade ≥3 severity), anaphylactic reaction had been reported in 0.8% during maintenance, but in 0.4% during up-dosing.

GI disorders (AEs Grade ≥ 3 severity) occurred mainly during up-dosing (1.0 %), but had not been reported during maintenance.

Data for systemic allergic reactions (MedDRA preferred term anaphylactic reaction) were reanalysed in consistent 13-week (i.e, quarter-annual) intervals out to 78 weeks, and were provided in response to the day 120 LOQ: Incidence of systemic allergic reactions did not appear to decrease over the course of the individual studies, neither did the severity of the systemic allergic reactions appear to change over the treatment course.

This observation is further supported in the day 180 responses: There is no indication that systemic allergic reactions decrease over time during up-dosing or maintenance.

The likelihood of developing a systemic allergic reaction is not associated with a certain study period.

Severe allergic reactions were rare during treatment, independent from study period.

The performance of an exposure-adjusted event rate for anaphylaxis for treatment phases is as follows:

Table 19 Summary of Exposure-Adjusted Systemic Allergic Reactions by Study Period (Controlled and Integrated Populations)

	IDE		Up-Dosing		300 mg/d, 0-26 wk		300 mg/d, 27-52 wk		300 mg/d, 53-78 wk		300 mg/d, > 78 wk	
	AR101	**Placebo**	**AR101**	**Placebo**	**AR101**	**Placebo**	**AR101**	**Placebo**	**AR101**	**Placebo**	**AR101**	**Placebo**
Controlled population												
4-17 years												
Total exposure-years	4.55	1.83	342.60	136.82	181.06	68.92	5.43	1.28				
Total event rate	6 (1.32)	1 (0.55)	87 (0.25)	10 (0.07)	43 (0.24)	4 (0.06)	0	0				
Severe event rate	0	0	4 (0.01)	0	1 (0.01)	0	0	0				
4-11 years												
Total exposure-years	3.04	1.28	229.94	95.35	124.23	48.71	4.17	0.96				
Total event rate	2 (0.66)	1 (0.78)	43 (0.19)	6 (0.06)	22 (0.18)	4 (0.08)	0	0				
Severe event rate	0	0	1 (0.00)	0	0	0	0	0				
12-17 years												
Total exposure-years	1.50	0.55	112.66	41.47	56.84	20.22	1.26	0.33				
Total event rate	4 (2.66)	0	44 (0.39)	4 (0.10)	21 (0.37)	0	0	0				
Severe event rate	0	0	3 (0.03)	0	1 (0.02)	0	0	0				
Integrated population												
4-17 years												
Total exposure-years	5.09		385.82		341.51		140.96		50.44		4.95	
Total event rate	6 (1.18)		96 (0.25)		77 (0.23)		30 (0.21)		9 (0.18)		2 (0.40)	
Severe event rate	0		4 (0.01)		1 (0.00)		5 (0.04)		0		0	
4-11 years												
Total exposure-years	3.42		259.66		238.60		99.27		36.63		3.19	
Total event rate	2 (0.59)		47 (0.18)		39 (0.16)		20 (0.20)		5 (0.14)		1 (0.31)	

Severe event rate	0		1 (0.00)		0		3 (0.03)		0		0	
12-17 years												
Total exposure-years	1.67		126.16		102.90		41.69		13.81		1.76	
Total event rate	4 (2.39)		49 (0.39)		38 (0.37)		10 (0.24)		4 (0.29)		1 (0.57)	
Severe event rate	0		3 (0.02)		1 (0.01)		2 (0.05)		0		0	

Shading indicates not applicable (no dosing after 52 weeks at 300 mg/day for the controlled population and no placebo group for the integrated population).
Total event rate includes systemic allergic reactions of any severity (mild, moderate, severe [anaphylaxis]).
Exposure-adjusted event rates were defined as the total number of events divided by the total number of subject-years at risk during the period.
D, day; IDE, initial dose escalation; wk, weeks.

Table 20 Systemic Allergic Reactions During 300 mg/day Dosing by Interval (Integrated Population)

	300 mg/day 0-13 weeks (N = 770)	300 mg/day 14-26 weeks (N = 700)	300 mg/day 27-39 weeks (N = 449)	300 mg/day 40-52 weeks (N = 249)	300 mg/day 53-65 weeks (N = 197)	300 mg/day 66-78 weeks (N = 76)
Subjects with ≥ 1 systemic allergic reaction	36 (4.7%)	27 (3.9%)	11 (2.4%)	10 (4.0%)	5 (2.5%)	3 (3.9%)
By maximum severity [1]						
Mild	18 (2.3%)	14 (2.0%)	3 (0.7%)	4 (1.6%)	2 (1.0%)	1 (1.3%)
Moderate	18 (2.3%)	12 (1.7%)	4 (0.9%)	5 (2.0%)	3 (1.5%)	2 (2.6%)
Severe (anaphylaxis)	0	1 (0.1%)	4 (0.9%)	1 (0.4%)	0	0
By no. of events						
1 Event	31 (4.0%)	25 (3.6%)	10 (2.2%)	8 (3.2%)	4 (2.0%)	2 (2.6%)
2 Events	4 (0.5%)	1 (0.1%)	1 (0.2%)	2 (0.8%)	1 (0.5%)	1 (1.3%)
3 Events	1 (0.1%)	1 (0.1%)	0	0	0	0
> 3 Events	0	0	0	0	0	0
Led to study product discontinuation	1 (0.1%)	1 (0.1%)	1 (0.2%)	0	0	0
By trigger [2]						
Study product	32 (4.2%)	24 (3.4%)	8 (1.8%)	7 (2.8%)	4 (2.0%)	1 (1.3%)
Food allergen (peanut)	2 (0.3%)	0	0	0	0	0
Food allergen (nonpeanut)	2 (0.3%)	3 (0.4%)	2 (0.4%)	2 (0.8%)	1 (0.5%)	1 (1.3%)
Nonfood allergen	1 (0.1%)	0	1 (0.2%)	1 (0.4%)	0	2 (2.6%)
Unknown	0	0	0	0	0	0

Denominators for percentages of subjects with ≥ 1 systemic allergic reaction were based on the number of subjects within each treatment group who were at risk during the corresponding study period.

[1] The 3-point European Academy of Allergy and Clinical Immunology (EAACI) grading scale was used for grading the severity of anaphylactic reactions.

[2] Subjects could be counted in multiple trigger categories.

When focusing on anaphylaxis, from those ten subjects who developed anaphylaxis, 7 were older than 10 years of age; 8 female and 2 male (Table 21).

Table 21 Summary of Subjects With Anaphylaxis

Study	Nb of Subjects	Age	Serious	Period, Study Day	Dose	Epi Use
ARC003	1	15	Yes	300 mg/day, 284	300 mg	Yes
ARC004	1	4	No	300 mg/day, 389	300 mg	Yes
ARC004	1	5	No	300 mg/day, 458	240 mg	No
ARC004	1	13	No	300 mg/day, 389	300 mg	Yes
ARC004	1	14	No	300 mg/day, 444	300 mg	Yes
ARC004	1	5	No	300 mg/day, 471	300 mg	Yes
ARC007	1	10	No	Up-dosing, 70	40 mg	Yes
ARC007	1	17	No	Up-dosing, 64	6 mg	Yes
ARC007	1	14	No	Up-dosing, 104	120 mg	No
ARC007	1	14	No	Up-dosing, 72	80 mg	Yes

Study day is from the first day of treatment. Epi, epinephrine.

Four subjects experienced anaphylaxis during up-dosing. All 6 subjects who developed anaphylaxis during maintenance experienced their symptoms after more than 40 weeks of treatment (starting study day 284).

According the applicant, eight of the 10 subjects who experienced anaphylaxis had potential cofactors like exercise and non-specific viral infections.

Laboratory findings

Generally, shifts in blood cell counts from baseline level to worst post-baseline level occurred rarely. However, a decrease of white blood cell (WBC) among 9% of Palforzia treated patients vs. 6% of placebo patients, an increase of eosinophils 15% Palforzia vs. 11% placebo, and a decrease of neutrophils 7% Palforzia vs. 4% placebo were noted. There were no clinically relevant differences between Palforzia treated patients and patients in the placebo group with regard to vital signs, lung function tests, and asthma control test.

Safety in special populations

The current application is limited to children 4-17 years of age and adolescents turning 18 years of age during treatment. Currently there are only limited data on adults (see below), and no data on elderly patients.

The data gained so far suspect a higher efficacy and better safety for younger individuals.

Children:

The presented results regarding TEAEs by subject age group and sex support this assumptions (Table 22): "In the integrated safety population overall, a higher proportion of subjects aged 4 to 11 years had mild adverse events compared with subjects aged 12 to 17 years (42.2% vs 33.8%) and a lower proportion had moderate (53.5% vs 59.2%) and severe (3.0% vs 5.8%) adverse events. A lower proportion of subjects aged 4 to 11 years had adverse events of systemic allergic reaction (11.9% vs 21.9%), and of 10 subjects with severe systemic allergic reaction (anaphylaxis, Table 41), 4 were in the 4 to 11 year age group.

Likewise study TEAEs leading to study product discontinuation are with 13.8% vs 10.2% higher in the older population (11-17 years of age).

Similar observation had been made for the controlled population.

Table 22 Overall Summary of Treatment-Emergent Adverse Events by Age Group and Sex (Palforzia (AR101) Overall Any Dose, Integrated Safety Population)

	Age Group		**Sex**	
	4-11 Years (N=630)	**12-17 Years (N=311)**	**Male (N=561)**	**Female (N=383)**
Total no. exposure-years	623.04	283.25	535.97	373.15
Total no. adverse events (exposure-adj)	27655 (44.4)	14467 (51.1)	24492 (45.7)	18016 (48.3)
No. (%) subjects with at least 1:				
Adverse event	623 (98.9%)	307 (98.7%)	554 (98.8%)	379 (99.0%)
By severity				
Grade 1: Mild	266 (42.2%)	105 (33.8%)	220 (39.2%)	153 (39.9%)
Grade 2: Moderate	337 (53.5%)	184 (59.2%)	319 (56.9%)	203 (53.0%)
Grade 3: Severe	19 (3.0%)	18 (5.8%)	15 (2.7%)	22 (5.7%)
Grade 4: Life-threatening	1 (0.2%)	0	0	1 (0.3%)
Grade 5: Death	0	0	0	0
Related to study product	562 (89.2%)	286 (92.0%)	502 (89.5%)	349 (91.1%)
Led to study product discontinuation	64 (10.2%)	43 (13.8%)	61 (10.9%)	47 (12.3%)
Systemic allergic reaction	75 (11.9%)	68 (21.9%)	80 (14.3%)	63 (16.4%)
Associated with non-study product food allergen exposure	121 (19.2%)	52 (16.7%)	93 (16.6%)	81 (21.1%)
No. (%) subjects with at least 1:				
Serious adverse event	10 (1.6%)	4 (1.3%)	7 (1.2%)	7 (1.8%)
By severity				
Grade 1: Mild	0	1 (0.3%)	0	1 (0.3%)
Grade 2: Moderate	5 (0.8%)	2 (0.6%)	5 (0.9%)	2 (0.5%)
Grade 3: Severe	4 (0.6%)	1 (0.3%)	2 (0.4%)	3 (0.8%)
Grade 4: Life-threatening	1 (0.2%)	0	0	1 (0.3%)
Grade 5: Death	0	0	0	0
By relationship to study product				
Not related	7 (1.1%)	2 (0.6%)	5 (0.9%)	4 (1.0%)
Related	3 (0.5%)	2 (0.6%)	2 (0.4%)	3 (0.8%)

In the context of the response to the day 120 List of questions, the applicant added subgroup analysis, which were defined as having the following baseline characteristics:

- ps-IgE (in quartiles):
  - < Q1 (30.9 kUA/L), ≥ Q1 to < Q2 (84.1 kUA/L), ≥ Q2 to < Q3 (205.0 kUA/L), and ≥ Q3 for subjects aged 4 to 11 years
  - < Q1 (32.1 kUA/L), ≥ Q1 to < Q2 (72.7 kUA/L), ≥ Q2 to < Q3 (172.0 kUA/L), and ≥ Q3 for subjects aged 12 to 17 years
  - < Q1 (31.5 kUA/L), ≥ Q1 to < Q2 (80.1 kUA/L), ≥ Q2 to < Q3 (193.3 kUA/L), and ≥ Q3 for subjects aged 4 to 17 years
- SPT reaction (in quartiles):
  - < Q1 (9.0 mm), ≥ Q1 to < Q2 (11.5 mm), ≥ Q2 to < Q3 (15.5 mm), and ≥ Q3 for subjects aged 4 to 11 years
  - < Q1 (9.5 mm), ≥ Q1 to < Q2 (12.5 mm), ≥ Q2 to < Q3 (16.5 mm), and ≥ Q3 for subjects aged 12 to 17 years
  - < Q1 (9.5 mm), ≥ Q1 to < Q2 (12.0 mm), ≥ Q2 to < Q3 (16.0 mm), and ≥ Q3 for subjects aged 4 to 17 years
- Reaction at baseline food challenge (screening DBPCFC) in groups:
  - 1 or 3 mg
  - 10 or 30 mg
  - 100 or 300 mg
- History versus no history of asthma
- History versus no history of allergic reaction to peanut (note, data on the *severity* of prior allergic reaction to peanut was not collected)

In the descriptive analysis trends have been noticed in all treatment phases in the treatment group indicating that expressed as a percentage, most systemic allergic reactions occurred in the age population of 12-17 year old subjects with higher ps-IgE levels (≥ Q2 to < Q3 and ≥ Q3). The analysis suggests, that these reactions stay present although patients received the maintenance phase (20-30 % of older subjects with ≥ 1 event in ARC003 and ARC010 during maintenance). Epinephrine episodes have been depicted especially in IDE and Up-dosing and maintenance of treated subjects. In subjects aged 12-17, these were nearly all indicated with a binary amount of events. Thus high allergic subjects were also those patients who discontinued during IDE or Up-dosing.)

Descriptive subanalysis (post-hoc) of study safety data of ARC003 and ARC010 have been presented – however, valid statistical conclusions may not be drawn. Focusing on safety, higher rates of systemic allergic reaction and epinephrine use have been observed in adolescent subjects and those with higher baseline IgE levels. Patients aged 12-17 experienced twice as many systemic allergic reactions including anaphylaxis than patients aged 4-11 years; 21.9% [95% CI: 17.3, 26.5%] vs. 11.9% (95% CI: 9.4, 14.4 %). In addition, 7/311 adolescents (2%) as compared to 3/630 patients younger than 11 years (0.5%) experienced anaphylaxis. These observations cannot (only) be explained by a more risk-prone behavior in teenagers as teenagers in the placebo-arm did not experience these events. Most systemic allergic reactions occurred during IDE and up-dosing, however, also during maintenance the risk of a systemic allergic reaction was approx. 10 times higher in the treatment arms than the placebo arms. Within responses at day 180 responses the applicant presented further analysis and "acknowledges that the incidence of systemic allergic reactions increases in adolescents and adults over younger children", please see Table ***23*** (including data from ARC003, ARC010 and in addition from ARC007):

Table 23 Summary of Systemic Allergic Reaction by Age Group (Controlled Studies)

Age at Inclusion Subjects with ≥ 1 event	IDE and Up-Dosing		ARC010 300 mg/day		ARC003 300 mg/day	
	AR101	Placebo	AR101	Placebo	AR101	Placebo
4-11 Years, N	335	119	83	28	205	84
	23 (6.9%)	1 (0.8%)	4 (4.8%)	1 (3.6%)	12 (5.9%)	2 (2.4%)
12-17 Years, N	169	48	25	13	105	34
	19 (11.2%)	1 (2.1%)	4 (16.0%)	0	15 (14.3%)	0
18-55 Years, N [1]	41	14	0	0	25	14
	4 (9.8%)	0	0	0	5 (20.0%)	1 (7.1%)

[1] Adult subjects were not eligible to enroll in study ARC010. IDE, initial dose escalation.

For all binary response endpoints and populations analyzed at day 180 responses, the majority of odds ratio point estimates are less than 2.0, though trends (ie, where OR > 2.0) suggest that older age (12-17 years vs 4-11 years) and increasing baseline levels of ps-IgE Ara h 2 may be more likely to be associated with these events: systemic allergic reactions, epinephrine use, and discontinuation from study due to persistent GI adverse events. In general, these results are remarkably clear, and the applicant confirms that a consistent pattern of predictors can be observed. In particular, treatment remains the strongest predictor of adverse events, after adjustment. Further, the applicant confirms that age ≥12 years consistently shows an association with higher odds for adverse events. Similarly, high baseline levels of ps-IgE Ara h 2 are associated with increased risk of adverse events.

Results suggest that Log10 ps-IgE/IgG4 ratio and ps-IgE Ara h 3 may also be predictive for Systemic Allergic Reactions and Epinephrine use, while an association of ps-IgE Ara h 9 and SPT with the odds for discontinuation due to GI adverse events was observed.

Subjects who turned 18 years during treatment:

The data of subjects who turned age 18 years during treatment with Palforzia is very limited. Only 8 subjects treated with Palforzia (4 with placebo). The safety profile of subjects who turned age 18 years during treatment in an Palforzia clinical study is consistent with the overall population of subjects aged 4 to 17 years. The applicant added supportive safety data from n=55 subjects ages 18-55 years (median age 23.0 years). From these population, seven subjects (17.1%) of Palforzia group (n=41) discontinued study product due to 1 or more events.

This discontinuation rate is higher than the discontinuation rate of younger patients, where 11.4% of subjects had 1 or more adverse events that led to study product discontinuation (controlled population). (Integrated population discontinuation 10.6%)

In both age subsets the discontinuation was higher during up-dosing than initial dose escalation and all 300 mg/day dosing.

Please see chapter "*Discontinuations due to AEs*" below.

Adults:

The overall pattern of adverse events and safety profile for adult subjects aged 18 to 55 years, who represented approximately 10% of the overall study population of subjects aged 4 to 55 years in study

ARC003, was consistent with the pattern observed in paediatric subjects aged 4 to 17 years. GI disorders and respiratory, thoracic, and mediastinal disorders were the most common system organ classes overall, and exposure-adjusted event rates generally decreased from up-dosing to maintenance. No adult subject had a grade ≥ 3 treatment-related adverse event, but 1 Palforzia-treated subject had a non-serious treatment-related severe symptom of urticaria during up-dosing. Two Palforzia-treated subjects and 1 placebo-treated subject had a serious adverse event, all during maintenance: 1 subject discontinued due to a moderate systemic allergic reaction considered treatment related and 1 subject continued study treatment after an event of severe syncope considered not related to study product. One placebo-treated subject had severe cutaneous vasculitis and continued study treatment. Eight Palforzia-treated subjects (19.5%) and 1 placebo-treated subject (7.1%) had 1 or more systemic allergic reactions; 2 of these subjects discontinued study treatment. Other discontinuations were primarily due to GI adverse events and symptoms during up-dosing. No adult subject experienced a severe systemic allergic reaction (anaphylaxis) or had a diagnosis of EoE.

Other intrinsic factors

Patients who previously experienced a systemic allergic reaction to peanut were more likely to experience a systemic allergic reaction. There were no differences in safety profile between patients with or without a history of atopic dermatitis

Pregnancy

Patients were required to avoid pregnancy during the studies. Hence, there are no data to clarify the benefits and risks of continuing treatment during pregnancy, e.g. if the tolerance to Palforzia changes during pregnancy. However, with life-long therapy it is expected that approximately half of the included population would ultimately have to decide whether or not to continue treatment during pregnancy.

Potential 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[36]. 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.

Use during pregnancy will be further characterised in a post-marketing pregnancy registry that will collect data on reports of exposure to Palforzia during pregnancy (see 2.6.1. safety discussion).

Overdose, drug abuse, withdrawal and rebound

Overdose may be associated with allergic reactions, including anaphylaxis. Drug abuse is not expected.

Study ARC004 addresses other application schedules of Palforzia than the daily schedule used in the presented studies. The final CSR ARC004 (finalised 14 Feb 2020) was submitted with the responses to the day 120 list of questions. First experiences with a small subset of subjects (ARC004), suggest, that the daily consumption of Palforzia is in favor, compared to a non-daily schedule.

So far no data is known, which addresses a possible re-Bound effect in patients who discontinued treatment.

When Palforzia treatment is discontinued an increased severity of allergic reactions (i.e. rebound) upon exposure to peanut could possibly occur compared with the severity of allergic reactions before or during treatment. The applicant considered that this is very unlikely due to the competitive inhibition

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

by IgG4 of antigen binding to IgE[37,38,39] 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 (i.e. rebound) following discontinuation of food OIT at any point during the process.

As there are no data which address a possible rebound effect in patient, who discontinued treatment, CHMP considered that possible rebound effect should be monitored in the follow-on open-label ARC008 study listed in the RMP (please see 2.6.1. safety discussion).

The applicant summarised Key Study Conclusions as follows:

Safety profile: A lower incidence of treatment-related adverse events was reported with QD maintenance dosing compared with nondaily dosing regimens. Overall, the safety profile was predictable and manageable by the subject or caregiver.

- All systemic allergic reactions in this study were nonserious and most were mild or moderate in severity, occurred within 2 hours after Palforzia dosing, and were manageable by the subject or caregiver with available medications. Five subjects (2.4%) in group 2 (2 in cohort 1 and 3 in cohort 3C) experienced a severe systemic allergic reaction (anaphylaxis) during QD dosing; 4 continued Palforzia treatment and completed the study.
- The use of dosing intervals longer than QD dosing with Palforzia was not well characterised due to the small numbers of subjects treated and relatively shorter exposure periods in nondaily dosing cohorts. While no specific safety concerns were noted with nondaily dosing, efficacy data from the DBPCFCs (response rates, single highest tolerated dose, maximum severity of symptoms) indicated that during the first 1 to 2 years of treatment, an overall trend toward favoring QD dosing to maintain or improve the effectiveness of desensitization.
- Treatment-related adverse events during continuing Palforzia maintenance treatment were readily manageable, mild or moderate allergic reactions. Throat irritation was the most common event during QD dosing overall (approximately 10% of subjects) and throat irritation and nausea were the most common events during nondaily dosing overall (approximately 20% in cohort 2 overall). The incidence of treatment-related adverse events was generally higher during BIW dosing than QD dosing.
- After adjusting for exposure, oral pruritus and throat irritation were the most frequent treatment-related adverse events during QD dosing overall, and throat irritation, upper abdominal pain, and oral pruritus were the most frequent treatment-related adverse events during nondaily dosing (cohort 2 overall). When adjusted for duration of exposure, treatment-related adverse events were generally more frequent during BIW dosing than QD dosing.
- The incidence of serious adverse events was low, and no subject had a treatment-related serious adverse event. No subject had a treatment-related life-threatening adverse event or died during the study.

[37] Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. J Allergy Clin Immunol. 2018;141(2):491-8.
[38] 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.
[39] 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.

- Severe adverse events and symptoms were infrequent, manageable, and resulted in no adverse sequelae.
- Epinephrine use did not correlate with the severity of the adverse events for which it was administered, and most events with epinephrine use required a single dose.
- EoE continues to be an important identified risk of peanut OIT and Palforzia treatment. Nonserious EoE was reported in 2 subjects (0.6%) aged 4 to 17 years and 1 subject (3.3%) aged 18 to 55 years. Severity was moderate for 1 subject and severe for 2 subjects (1 during up-dosing, not related to Palforzia). Symptoms resolved during follow-up after discontinuation of Palforzia.

In all the small number of participants is to be considered.

Immunological events

For this drug product the immunomodulatory effect is the treatment effect. No undesired immunological events occurred.

Safety related to drug-drug interactions and other interactions

No potential drug or food interactions with Palforzia are known. Palforzia is intended to be taken with food, mixed in a soft food matrix for dosing.

The concomitant use of medicinal products known to interfere with the effect of epinephrine was excluded from Palforzia clinical studies to ensure that subject safety was not compromised if the use of epinephrine was required. Beta-adrenergic blockers antagonise the cardiostimulating and bronchodilating effects of epinephrine and alpha-adrenergic blockers antagonise the vasoconstricting and hypertensive effects of epinephrine.

The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, and monoamine oxidase inhibitors.

Further, it is recommended that other types of AIT are not initiated during the up-dosing phase of Palforzia OIT.

Discontinuation due to adverse events

In the controlled population, AEs led to discontinuation in 10.9% of subjects in the Palforzia group and 2.4% in the placebo group. Most common system organ class of AEs leading to discontinuation were associated with GI disorders during initial dose escalation and up-dosing (7.6% Palforzia, 0.9% placebo). These disorders were characterised by abdominal pain (3.7%Palforzia, 0.3% placebo), vomiting (3.0%, 0%), nausea (2.1% Palforzia, 0% placebo), and systemic allergic reaction, including anaphylaxis (1.4% Palforzia, 0% placebo). Systemic allergic reaction led to discontinuation in 2 subjects (1 had anaphylaxis) during 300 mg/day dosing in study ARC003.

In the integrated safety population, 108 subjects (11.4%) discontinued study product. The AEs leading to discontinuation of study product were consistent with the controlled population and the majority of subjects discontinued during up-dosing (8.7%) followed by initial dose escalation (2.1%) and all 300 mg/day dosing (1.2%).

Correspondent data were gained in study ARC007 were 20 Palforzia-treated subjects discontinued from the study due to chronic/recurrent GI adverse events. However, GI adverse events resolved in up to 2

weeks for 17 of 20 subjects, between 2 and 4 weeks in 2 subjects, whereas the time to resolution was unknown for 1 subject. These data suggest, that GI symptoms resolved when stopping Palforzia intake.

Of note: Discontinuation due to an AE is only one aspect. Other reasons for discontinuations included 'Dosing Symptom' 3%, 'Withdrew consent' 6%, 'Sponsor decision' 1%, and 'Other' 2%. The applicant has as adequately as possible clarified the reasons for discontinuation that was not specifically due to AEs. Overall, approximately 22% of patients treated with Palforzia discontinued the studies while only approximately half of these were reported to be due to AEs. However, it appears that the majority of the other discontinuations are likely to be related to the Palforzia treatment as well, e.g. discontinuation due to dosing symptoms, which are described as "allergic reactions observed after dosing with the study product during supervised dosing at study sites" (2.7% of all Palforzia patients). Furthermore, most patients who withdrew consent where noted to have mild or moderate AEs around the time of the withdrawal (6% of all Palforzia patients). In the placebo group, 7% discontinued treatment. Thus, overall it could be concluded that approx. 15% of the patients treated with Palforzia discontinued specifically due to reactions to the study product.

When considering the entire population of 1182 Palforzia-treated subjects aged 4 to 55 years in the integrated population overall 42.6% discontinued from treatment as follows:

42.6% any reason, 14.3% adverse event/symptom, 21.1% withdrew consent

4 to 11 years: 37.7% any reason, 13.1% adverse event/symptom, 18.2% withdrew consent

12 to 17 years: 49.6% any reason, 15.3% adverse event/symptom, 26.3% withdrew consent

18 to 55 years: 63.6% any reason, 23.6% adverse event/symptom, 25.5% withdrew consent

A total of 430 subjects were still receiving Palforzia in the ongoing study ARC008 as of the latest data cutoff (03 Jun 2020) and discontinuations so far were noted out to day 1345 (ie, after 3.7 years of Palforzia treatment).

Presented data within the day 120 responses depict that in ARC004 group 1 (former placebo-treated subjects from study ARC003), only 55 of 102 subjects (53.9%) completed the study and 47 subjects (46.1%) discontinued early. In the day 180 responses, the applicant explained that the most common reason for early discontinuation in ARC004 group 1 was withdrawal of consent (31.4%). Of the 32 subjects who withdrew consent, 14 were aged 4 to 11 years and 18 were aged 12 to 17 years, so proportionally, the rate of voluntary withdrawal of consent was again higher in the adolescent age group. Thus, withdrawal of consent in this ARC004 group of 102 formerly placebo-treated subjects was considerably higher than the withdrawal of consent rate of 10.8% for the integrated population.

Post marketing experience

Palforzia was approved in the United States on 31 January 2020. No post-marketing experience have been provided.

2.6.1. Discussion on clinical safety

Summary of safety data

Safety data have been reviewed for the integrated safety population, including 944 subjects from 5 clinical studies (ARC003, ARC007, ARC010, ARC004, ARC011) who received at least 1 dose of Palforzia, including 770 subjects who received the maintenance dose of 300 mg/day. Approximately one-fourth of subjects were enrolled in Europe. The safety database is considered adequate.

The most relevant safety data derived from the combined controlled population, which compromised 841 subjects treated with Palforzia and 335 subjects treated with placebo, from the 3 randomised controlled phase 3 clinical trials (ARC003 (Europe and North America), ARC007 (North America only), ARC010 (Europe only)) data cut-off date 15 Dec 2018.

Data from 2 phase 2 studies ARC001 and ARC002 as well as from uncontrolled, follow-on studies (ARC004 and ARC011) (data cut-off date 15 Dec 2018) provided further supportive data on long-term safety. It is noted that a subset of patients, Group 2 Cohort 2, in the extension study ARC004 submitted during the evaluation, were excluded from the safety analyses.

In above presented populations, subjects in the Palforzia group were treated for a median of 2.0 days during initial dose escalation, and during up-dosing for a median of 154.0 days (22 weeks). In the integrated safety population, 81.6% of subjects reached the maintenance dose of 300 mg/day and were treated for a median of 27 weeks overall, and with any dose of Palforzia for approximately 49 weeks overall. The longest treatment with Palforzia was in subjects who received Palforzia in the phase 2 study ARC001 and continued treatment in the follow-on study ARC002 (median exposure approximately 3 years). Patients in phase 3 studies have been followed for a maximum of two years (n=26) by the latest cut-off date. Thus, no recommendation is currently possible beyond 24 months; this is adequately reflected in the SmPC.

With this population, the ICH E1 safety exposure requirements of 300 to 600 patients for 6 months, respectively > 100 patients for 1 year are fulfilled.

In general, baseline demographic characteristics were similar and adequately balanced among treatment groups (active-placebo).

Discontinuations and treatment duration

In the overall placebo-controlled population of subjects aged 4 to 55 years (882 Palforzia, 349 placebo as of 03 Jun 2020), 22.9% Palforzia and 6.6% placebo patients discontinued from studies for any reason. The primary reason for discontinuation was adverse events or symptoms for 12.1% Palforzia and 2.3% placebo and withdrawal of consent for 6.9% Palforzia and 2.9% placebo.

Discontinuations due to adverse events or symptoms in the overall population were higher during up-dosing (9.7% Palforzia, 1.2% placebo) and substantially lower during maintenance (0.7% Palforzia, 0.3% placebo). It should be noted that the maintenance period in the controlled studies was relatively short (approximately 2 weeks in ARC007, 3 months in ARC010, and 6 months in ARC003). Withdrawal of consent was also higher during up-dosing (4.9% Palforzia, 2.0% placebo) than maintenance (2.1% Palforzia, 0.9% placebo).

When discontinuations are considered by age group (4-11 years, 12-17 years, 18-55 years), overall discontinuations increased by age group. Within each group, discontinuations due to adverse events or symptoms and withdrawal of consent were higher during up-dosing and substantially lower during maintenance except in the 18 to 55 years group, where withdrawal of consent was similar between up-dosing and maintenance (15.4%, 16.0%).

A similar trend was observed considering the entire population of 1182 Palforzia-treated subjects aged 4 to 55 years in the integrated population. Overall 42.6% discontinued from treatment for any reason, 14.3% due to adverse event/symptom and 21.1% withdrew consent and discontinuations increased by age (see also section 'Discontinuation due to AEs').

A total of 430 subjects were still receiving Palforzia in the ongoing study ARC008 as of the latest data cutoff (03 Jun 2020) and discontinuations so far were noted after 3.7 years of Palforzia treatment. As there are no data which address a possible rebound effect in patient, who discontinued treatment, CHMP considered that possible rebound effect should be monitored in the follow-on open-label ARC008

study listed in the RMP. In addition, possible rebound effect after discontinuation of treatment is added as an important potential risk in the RMP.

Common adverse events

Overall TEAEs for the integrated safety and for the controlled population are comparable. The incidence of adverse reactions was higher during up-dosing (85.7%) than initial dose escalation (45.1%) and maintenance (57.7%). During the initial dose escalation and up-dosing phase, abdominal pain (53%), throat irritation (42%), pruritus (37%), vomiting (37%), nausea (36%), and cough (34%) were most common among Palforzia treated individuals. During the maintenance phase, abdominal pain (15-22%), urticaria (20%), pruritus (15-22%), cough (19-20%), and oral paraesthesia (7-17%) were most common among Palforzia treated individuals.

Based on the observations on the increased incidence of reactions during the initial dose escalation and up-dosing phases, there is a risk that during up-dosing a patient may be exposed to higher dose escalations due to the possible differences in potencies between the batches. This is especially a concern during the up-dosing phase, where patients have not yet developed a reasonable tolerance to peanut protein. 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. This is reflected in section 4.2 of the SmPC.

Systemic allergic reactions (anaphylactic reactions)

The main risk associated with treatment with Palforzia is a systemic allergic reaction, which occurred in 15.1% of the population, including 0.6% during initial dose escalation, 8.7% during up-dosing, and 9.9% during maintenance. The majority of patients experienced a single event but 3% of the total population experienced two or more anaphylactic reactions.

Anaphylaxis, defined as a severe systemic allergic reaction, 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; 1 patient had a serious event. All subjects recovered and none required prolonged hospital admission or required intensive support with antihypotensive medication or intubation. Six subjects continued study treatment and 4 discontinued from their study. Eight of the 10 subjects who experienced anaphylaxis had potential cofactors.

Most allergic reactions occurred during the initial dose escalation and up-dosing phases. However, during the maintenance phase, the risk of anaphylactic reactions remained approximately ten times higher in the treatment than the placebo group. Even when looking at subjects who are on maintenance for as long as 66-78 weeks, incidence of systemic allergic reactions did not appear to decrease over the course of the individual studies, neither did the severity of the systemic allergic reactions appear to change. Nevertheless, these reactions mostly occur during the first 2 hours after ingestion of the dose and are usually mild or moderate.

CHMP considered that the induction of allergic reactions due to daily contact with the allergen was expected, as well as the observation that adverse events were in general higher during up-dosing than initial dose escalation and maintenance. Furthermore, it is accepted that patients only on peanut free diet suffer much less from allergic reactions. Different multivariate analysis documented again that treatment per se; age and sensitization are associated with increased risk for adverse events.

In the CHMP's view, the risk of allergic reaction is adequately addressed in the section 4.2 of the SmPC which recommends that the initial dose escalation and the first dose of each new up-dosing level are administered in a health care setting prepared to manage potential severe allergic reactions. In addition, self-injectable adrenaline (epinephrine) must be available to the patient at all times.

It is also acknowledged that 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. Furthermore, non-adherence to daily treatment, also during subsequent years of maintenance, seems to increase the risk of adverse allergic reactions. Therefore, adequate guidance on the management of co-factors have been added in section 4.2 and 4.4 of the SmPC.

In general, the complexity within Palforzia treatment (including dose modification upon individual cases of intercurrent events like stress, alcohol consumption, viral illness, menses or others) likely exposes patients to additional risk as it may be difficult to comply with the elaborate rules and its feasibility of transmission to real-life settings. At the CHMP's request, the applicant adequately revised the instructions and recommendations in the SmPC. Nevertheless, it is acknowledged that treatment regimen requires commitment, active participation and a shared-decision making between the patient, its family and the treating physician and that Palforzia treatment will not be suitable for all patients with peanut allergy. Healthcare professional and patients/caregivers educational materials and a patient card have been created to provide education and counselling regarding the appropriate use, adverse reactions and their management, and when to seek medical care.

Furthermore, appropriate risk minimisation measures have included in the SmPC to manage the risk of systemic anaphylactic reactions such as special warnings and precautions for use (sections 4.2, 4.3, 4.4 and 4.8 of the SmPC). The package leaflet is updated accordingly. Anaphylaxis/systemic allergic reactions is also listed as an important identified risk in the RMP. Furthermore, additional pharmacovigilance activities are performed to further collect safety data on the risk of anaphylactic reaction from the ongoing open-label extension for maintenance of desensitization and safety study (ARC008). In addition, the risk is reflected in the healthcare professional education materials and patient and parent/caregiver educational materials as mentioned above.

CHMP also noted that up to now, no markers or special patient characteristics are evident, which may predict if an individual patient would suffer from more and/or more severe allergic adverse effects. Sub analysis (post-hoc) of study safety data suggest that a consistent pattern of predictors can be observed. In particular, treatment remains the strongest predictor of adverse events, after adjustment. Furthermore, the applicant confirms that age ≥12 years consistently shows an association with higher odds for adverse events. The section 4.4 of the SmPC includes that patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment. Similarly, high baseline levels of ps-IgE Ara h 2 are associated with increased risk of adverse events. Results suggest that Log10 ps-IgE/IgG4 ratio and ps-IgE Ara h 3 may also be predictive for systemic allergic reactions and epinephrine use, while an association of ps-IgE Ara h 9 and SPT with the odds for discontinuation due to GI adverse events was observed. However, no individual baseline factor is sufficiently strong to warrant withholding Palforzia treatment from adolescent patients with peanut allergy.

Eosinophilic esophagitis and other gastrointestinal disorders

The second main safety risk associated with Palforzia is eosinophilic oesophagitis. In clinical trials, 12 out of 1,217 subjects were diagnosed with biopsy-confirmed eosinophilic oesophagitis while receiving Palforzia compared with 0 of 443 subjects receiving placebo. After discontinuation of Palforzia, symptomatic improvement was reported in 12 of 12 subjects. In 8 subjects with available follow-up biopsy results, eosinophilic oesophagitis was resolved in 6 subjects and improved in 2 subjects.

Other gastrointestinal disorders were the most common adverse events observed, the leading term was abdominal pain, followed by vomiting, and nausea. Abdominal pain was described in the highest rates during up-dosing (Palforzia 415 (49.3%), Placebo 59 (17.6%); (Controlled Population)). Although reducing to 3.4% - 9%, abdominal pain was still present during maintenance. When focusing on AEs Grade ≥3 severity, especially gastrointestinal disorders had been reported (1.1%) in 818 Palforzia treated subjects. Again, GI AEs occurred more often during up-dosing than during maintenance therapy.

For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia), the potential for a diagnosis of eosinophilic oesophagitis should be considered. In patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, gastroesophageal reflux, chest pain, or abdominal pain, treatment must be discontinued and a diagnosis of eosinophilic oesophagitis should be considered. This is adequately reflected in the SmPC.

"A history of, or current, eosinophilic oesophagitis; other eosinophilic gastrointestinal disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); dysphagia" are contraindications to the use of Palforzia. A warning about gastro-intestinal adverse reactions including eosinophilic oesophagitis is also included in section 4.4 of the SmPC to inform about the risk and to provide instructions if patients develop chronic or recurrent gastrointestinal symptoms. Eosinophilic oesophagitis is listed in section 4.8 of the SmPC as an adverse reaction with a frequency uncommon. The package leaflet is updated accordingly. In addition, it is listed an important identified risk in the RMP. Furthermore, eosinophilic oesophagitis will be further monitored in the ongoing open-label extension for maintenance of desensitization and safety study (ARC008).

Age

The data gained so far suggest an age-dependent effect. Additional statistical analysis provided by the applicant documented that age ≥12 years consistently shows an association with higher odds for adverse events. The same was true for certain sensitization parameters at baseline. The section 4.4 of the SmPC includes that patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment (see also 'Safety in special population' section).

There is limited data available in subjects turning 18 years of age while being on treatment with Palforzia. In total, 51 subjects were enrolled at age ≤ 17 years and subsequently turned age 18 during treatment with Palforzia. The applicant reported that nearly two-thirds of these subjects continue to be treated in study ARC008, some with cumulative treatment of more than 3 years.

In ARC003, safety data is derived from 55 subjects aged 18-55 years (median age 23.0 years). From these population, 7 subjects (17.1%) in Palforzia group (n=41) discontinued study product due to 1 or more events. In general the overall pattern of adverse events and safety profile for adult subjects aged 18 to 55 years in study ARC003 was consistent with the pattern observed in paediatric subjects aged 4 to 17 years.

As observed for the paediatric population, discontinuation rate as well as number of systemic allergic reactions was higher in adults compared to younger patients.

Interactions and Laboratory results

No direct interactions are expected with Palforzia nor have they been investigated. Nevertheless, peanut OIT is not recommended while undergoing other types or allergen immunotherapy.

Further, specific conditions (e.g. chronic lung disease) or treatments making the patient either unresponsive to treatment of anaphylaxis (e.g. beta-blockers) or more susceptible to adverse reactions

during treatment with epinephrine (e.g. TCAs) are addressed in the SmPC. The SmPC text regarding interactions is considered sufficient.

Impact on long-term immune-mediated reactions

Long-term data on the incidence of immune-mediated reactions such as anaphylactic reactions and eosinophilic esophagitis are available for 103 subjects and 26 subjects who completed 12 and 18 months respectively of Palforzia maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both ARC003 and the open-label, follow-on ARC004 study. The impact on long-term immune-mediated reactions beyond this period are limited. Therefore this safety concerns is listed as missing information in the RMP and the impact on long-term immune-mediated reactions will be further characterised through the open label, longer-term follow-on study (ARC008) 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.

Use during pregnancy

Patients who were pregnant were not treated with Palforzia in the clinical studies. Potential 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. 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. Therefore, a statement that indicate that there are no data on the clinical experience of Palforzia in pregnant women is included in section 4.6 of the SmPC. A warning that Palforzia should not be initiated during pregnancy is also included in section 4.6 of the SmPC and guidance for the patient no to start treatment with Palforzia if she is pregnant or planning to become pregnant and to ask her doctor for advice is included in section 2 of the package leaflet. 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 is also included in section 4.6 of the SmPC. Use during pregnancy is listed as a missing information in the RMP and pregnancy outcomes in pregnant women exposed to Palforzia ascertained by spontaneous reporting will be monitored in a post-marketing pregnancy registry as listed in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

2.6.2. Conclusions on the clinical safety

The safety data coming from 5 completed clinical studies as well as updated analysis of ongoing follow-up studies is considered adequate to characterise the safety profile in the target population of patient 4-17 years and subjects turning 18 years during treatment.

The most common adverse reactions observed in clinical trials were related to allergic reactions with systemic allergic reactions (anaphylactic reactions) being the main safety risk associated with Palforzia treatment. Most reactions occurred during the up-dosing and initial dose escalation phases. Existing data suggest that patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment. Systemic allergic reaction was also one of the reasons for discontinuation of treatment in 1.6% of the case.

The induction of allergic reactions due to daily contact with the allergen was expected, as well as the observation that adverse events were in general higher during up-dosing than initial dose escalation and maintenance. In addition, the complexity within Palforzia treatment is acknowledged as it likely

exposes patients to additional risk and it may be difficult to comply with the elaborate rules and its feasibility of transmission to real-life settings. Treatment regimen requires commitment, active participation and a shared-decision making between the patient, its family and the treating physician and it is acknowledged that Palforzia treatment will not be suitable for all patients with peanut allergy. Appropriate warnings and instructions are included in the product information. They are considered adequate by the CHMP and are regarded as helpful for daily use. Systemic anaphylactic reactions will be further monitored in a post-authorisation safety study. CHMP considered that appropriate risk minimisation measures have been put in place and careful selection of patients are expected to make the risks manageable through appropriate guidance in the SmPC and educational materials.

Although few cases were reported (1% of patient with Palforzia, 0 with Placebo), eosinophilic oesophagitis was identified as the second most important safety risk associated with Palforzia treatment. Oesophagitis; other eosinophilic gastrointestinal disease are therefore been added as contraindications to the use of Palforzia and special warning and instructions for use have been added in the product information. Eosinophilic oesophagitis will be further monitored in the post-authorisation safety study (ARC008). CHMP considered that appropriate risk minimisation measures have been put in place to manage the risk.

The age group 12 to 17 years consistently shows an association with higher odds for adverse events, but adverse events are mostly predictable and occurring in close proximity to dose administration. Adequate SmPC recommendation allowing for careful selection of patients who can receive Palforzia treatment are expected to adequately mitigate any additional risk. Based on the data provided, the CHMP also agreed that safety and efficacy are comparables in subjects turning age 18 on Palforzia treatment.

In conclusion, the safety profile of Palforzia in the claimed indication is considered acceptable by the CHMP.

2.7. Risk Management Plan

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

Pharmacovigilance plan

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 AR101 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	Q1 2021
Post-marketing pregnancy registry Ongoing in US	To monitor pregnancy outcomes in pregnant women exposed to AR101 ascertained by spontaneous reporting	Use during pregnancy	Annual registry reports are planned Final study report	The data lock will be based on the IBD and submission will coincide with the PSUR cycle June 2025

Study name Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 (4-11 year old patients) understanding and retention of core educational messages • Patient's (12-17 year old) understanding and retention of core educational messages • Monitor adherence to educational materials distribution plan	Anaphylaxis/ systemic allergic reactions Eosinophilic oesophagitis	Status updates Final study report	Status updates will be included in PSURs December 2025

Risk minimisation measures

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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *AE follow-up questionnaire for adverse reaction*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials*	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*
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*

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 31.01.2020. The new EURD list entry will

therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that defatted powder of *Arachis hypogaea* L., semen (peanuts) has been previously authorised in a medicinal product in the European Union but differs significantly with regard to safety and/or efficacy due to differences in molecular structure, nature of the source material or manufacturing process.

Based on the available quality and clinical data, the CHMP considers, that defatted powder of *Arachis hypogaea* L., semen (peanuts), which have some differences in molecular structure, nature of the source material or manufacturing process, does not differ significantly in properties with regard to safety and/or efficacy from medicinal products previously authorised within the European Union and therefore is not considered to be a new active substance.

A clear clinical argumentation for a new active substance claim regarding significant differences in terms of efficacy and safety has not been given by the applicant. Therefore, the active substance defatted powder of *Arachis hypogaea L., semen* (peanuts) contained in the medicinal product Palforzia is not to be qualified as a new active substance in comparison to the known active substances previously authorised in the European Union as medicinal products for skin prick testing as it was not shown to differ significantly in properties with regard to safety and efficacy from the previously authorised substance.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

Not applicable

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Palforzia (defatted powder of *Arachis hypogaea* L., semen (peanuts)) is included in the additional monitoring list as it is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Peanut allergy is a potentially life-threatening disease that disproportionately affects children, resolving in only approximately 20% of affected individuals[2]. In Europe, the prevalence of peanut allergy in children is approximately 1.6% as estimated by food challenges or clinical history[1].

IgE-mediated peanut sensitisation typically begins in infancy and progresses to a symptomatic allergy with increasing age. In most patients, peanut allergy is life-long. Some studies have reported that approximately 20% of children diagnosed with peanut allergy outgrow it[7,8,9]. Another study confirmed peanut allergy by food challenge in patients aged 1 year and reported resolution of peanut allergy in 22% of patients by age 4 years[10]. In patients who become tolerant to peanut, resolution of peanut allergy usually occurs by age 6 years and at a much lower frequency after age 10 years[11].

Peanut allergy is the most common cause of anaphylaxis and death related to food. Unintended food allergen exposures are common, with 55% of patients with peanut allergy reporting at least 1 allergic reaction over approximately 5 years[18]. Allergic responses may be triggered by minute quantities (< 5 mg) of peanut protein in individuals with peanut allergy [13]. Factors associated with life-threatening allergic reactions to peanut include a history of anaphylaxis to peanut, comorbid conditions (e.g., asthma, cardiovascular disease, systemic mastocytosis), the presence of a medical event such as intercurrent illness (e.g., viral infection), or the presence of other cofactors that may decrease the threshold for allergic reaction following allergen exposure (e.g., menstruation, stress, fatigue, sleep deprivation, exercise, increased body temperature, intake of NSAIDs, and alcohol use)[40]. Risk-taking behaviour in teenagers and young adults, such as failure to avoid triggers, failure to carry an epinephrine auto-injector, and alcohol use are thought to contribute to severe or fatal anaphylaxis[4]. The severity of chronic atopic disease such as asthma has been associated with the severity of peanut-induced acute allergic reactions[41]. As multiple factors can influence the severity of an allergic reaction, the severity of a reaction after unintended allergen exposure can be unpredictable [42,43].

Although death from food-induced anaphylaxis is rare, the burden of avoidance and constant fear of unintended exposure can negatively affect the health-related quality of life for individuals with food allergies and their families[20,12,21,22].

3.1.2. Available therapies and unmet medical need

No licensed therapeutic option is available for use in routine clinical practice for the treatment of people with peanut allergy in the EU. Current standard of care includes strict avoidance of peanut and treatment for allergic reactions following exposure. Exposure to peanut is inherently unpredictable, and the risk of severe, life-threatening, or even fatal allergic reactions increases when access to medical care and epinephrine are not readily available[3].

[40] Muñoz-Cano R, Pascal M, Araujo G, Goikoetxea, G, Valero AL, Picado C, et al. Mechanisms, cofactors, and augmenting factors involved in anaphylaxis. Front Immunol. 2017;8:1193.
[41] Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. J Allergy Clin Immunol. 2008;121(3):632-8.
[42] Pouessel G, Turner PJ, Worm M, Cardona V, Deschildre A, Beaudouin E, et al. Food-induced fatal anaphylaxis: from epidemiological data to general prevention strategies. Clin Exp Allergy. 2018;48(12):1584-93.
[43] Turner PJ, Baumert JL, Beyer K, Boyle RJ, Chan CH, Clark AT, et al. Can we identify patients at risk of life-threatening allergic reactions to food? Allergy. 2016;71(9):1241-55.

An important part of management of peanut allergy is education of the patient and family on the recognition and management of allergy symptoms and appropriate use of rescue medications (e.g., antihistamines, epinephrine auto-injectors). Prompt treatment with intramuscular epinephrine is the first-line treatment for anaphylaxis[23].

However, possession of epinephrine auto-injectors and their emergency use for anaphylaxis may also be inadequate, and may lead to adverse outcomes including hospitalisation and death[24]. Delay of rescue treatment can lead to severe and fatal allergic reactions[3].

Patients with peanut allergy are required to follow a strict peanut-avoidant diet, which can be difficult, imposes a significant negative quality-of-life burden on the patient and the patient's family and is a limited option to address the condition [20,12,21,22]. Strict adherence to an avoidance diet can be complicated by difficulty in interpreting food labels[44,14], the presence of undeclared or inadvertent introduction of allergens in commercially prepared foods[15,16], and inattention to or mistrust of food warning labels [17]. Foods prepared outside the home (e.g., at school, day care centres, restaurants, homes of family/friends) present additional potential sources of exposure.

Despite efforts at strict peanut avoidance, unintended exposure remains a major concern because allergic responses may be triggered by milligram doses of peanut protein. In a recent study conducted in the Netherlands, individuals with food allergy (including peanut) were provided counselling on an appropriate food-avoidance diet and were prospectively followed for 1 year. Despite counselling and education, 46% of patients reported an allergic reaction after unintended exposure and of these, 55% were patients with peanut allergy[45]. The mean number of reactions after unintended exposure was approximately 1 per person per year.

In 2018, the EAACI published guidelines on allergen immunotherapy for IgE-mediated food allergy[46]. During the development of this guideline, the EAACI conducted a formal systematic review and meta-analyses of randomised controlled studies of allergen immunotherapy in food-allergic individuals[47]. For OIT, these analyses defined a quantifiable benefit for desensitisation and a quantifiable risk of systemic allergic reactions. This benefit-risk assessment was considered favourable by the EAACI, and subsequently led to the recommendation of OIT for treatment of children with peanut allergy aged 4 years and older. However, several gaps have been identified by EAACI, e.g., lack of a standardised product with documented dosing regime, efficacy and safety.

Given the risk of life-threatening allergic reactions and lack of any licensed therapy for patients with peanut allergy, there is an unmet need for new therapies that reduce the incidence and severity of allergic reactions, including anaphylaxis, after exposure to peanut.

Palforzia has been developed to address this unmet medical need. Palforzia results are consistent with the benefits and risks to those considered favourable in the EAACI guideline. Notably, the Palforzia development program addresses many of the data gaps identified by EAACI, in that it provided a standardised product, a dosing protocol that has been assessed in 2 large randomised controlled studies, and a comprehensive assessment of safety during both up-dosing and maintenance.

[44] Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, van Duijn G, de Zeeuw-Brouwer ML, Versluis A, et al. Accidental food allergy reactions: products and undeclared ingredients. J Allergy Clin Immunol. 2018;142(3):865-75.
[45] Michelsen-Huisman AD, van Os-Medendorp H, Blom WM, Versluis A, Castenmiller JJM, Noteborn HPJM, et al. Accidental allergic reactions in food allergy: causes related to products and patient's management. Allergy. 2018;73(12):2377-81.
[46] Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799-815.
[47] Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017;72(8):1133-47.

3.1.3. Main clinical studies

The Palforzia clinical development program in children, adolescents, and adults with peanut allergy included 2 phase 2 studies (ARC001, ARC002) and 7 phase 3 studies (ARC003, ARC004, ARC005, ARC007, ARC008, ARC010, ARC011). During the evaluation, study ARC004 (open-label follow-on ARC003 study) was completed and the final clinical study report was assessed during the procedure.

In all Palforzia clinical studies, efficacy was measured using a DBPCFC. This food challenge was performed according to the Practical Allergy (PRACTALL) guidelines with modification to include a 600 mg protein dose (between the 300 mg and 1000 mg challenge doses).

The efficacy of Palforzia was assessed in 2 randomised, double-blind, placebo-controlled, multicentre, phase 3 pivotal studies ARC003 (PALISADE) and ARC010 (ARTEMIS). Both studies recruited subjects with a documented history of peanut allergy. Subjects with a severe or life-threatening anaphylaxis event within 60 days of study entry and those with severe or uncontrolled asthma were excluded from the studies. After an initial dose escalation ranging from 0.5 mg to 6 mg on day 1 and confirmation of tolerability of the 3 mg dose on day 2, subjects underwent up-dosing for 20 to 40 weeks starting at 3 mg until the 300 mg dose was reached. The up-dosing period varied for each subject depending on doses tolerated. Subjects then underwent 6 months (ARC003) or 3 months (ARC010) of maintenance immunotherapy with 300 mg Palforzia or placebo until the end of the study when subjects completed an exit DBPCFC to assess desensitisation to peanut.

ARC003 recruited subjects aged 4 to 55 years in Europe and North America. A total of 750 subjects aged 4 to 17 years were screened and 499 were randomly assigned (3:1) to study treatment (374 to Palforzia and 125 to placebo). ARC010 recruited subjects aged 4 to 17 years of age in Europe. A total of 175 subjects aged 4 to 17 years were randomly assigned (3:1) to study treatment (132 to Palforzia and 43 to placebo).

3.2. Favourable effects

The results of the pre-specified analyses of the primary and key secondary efficacy endpoints of the 2 pivotal, double-blind, placebo-controlled phase 3 studies ARC003 and ARC010 demonstrate statistical significance and consistency. The primary efficacy endpoint (proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC) was met in both studies ARC003 and ARC010. Treatment with Palforzia in the ITT population (4-17 years) resulted in statistically significant treatment effects over placebo, with treatment differences of 47.8% ($p < 0.0001$) in ARC003 and 56.0% ($p < 0.0001$) in ARC010.

Favourable treatment effects were also observed for key secondary endpoints of desensitization response and maximum severity of symptoms for subjects aged 4 to 17 years. These outcomes were further confirmed by supportive and sensitivity subgroup analyses and by sensitivity analyses using predefined analysis populations and worst-case imputation methods.

In the completer population of subjects aged 4 to 17 years, the proportion of subjects who tolerated a single dose of 1000 mg peanut protein at the exit DBPCFC with no more than mild symptoms was 63.2% for Palforzia-treated subjects in ARC003 and 72.6% in ARC010.

The proportion of subjects in the completer population who tolerated a single dose of 600 mg and 300 mg peanut protein with no more than mild symptoms were 84.5% and 96.3%, respectively in ARC003, and 84.9% and 91.5%, respectively, in ARC010.

In addition, the maximum severity of symptoms at any challenge dose during the exit DBPCFC for subjects aged 4 to 17 years in the ITT populations of ARC003 and ARC010 was reduced in the Palforzia group compared with placebo. In ARC003, the maximum severity of symptoms among treated subjects was no symptoms (37.6% Palforzia, 2.4% placebo), mild symptoms (32.0%, 28.2%), moderate symptoms (25.3%, 58.9%), and severe symptoms (5.1%, 10.5%). In ARC010, the maximum severity of symptoms was no symptoms (35.6% Palforzia, 0% placebo), mild symptoms (41.7%, 37.2%), moderate symptoms (18.2%, 46.5%), and severe symptoms (4.5%, 16.3%).

Moreover, fewer subjects treated with Palforzia used epinephrine as a rescue medication at the exit DBPCFC compared with subjects treated with placebo despite similar epinephrine use at the screening DBPCFC.

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

Sustained efficacy has been demonstrated in 102 subjects and 26 subjects who completed 12 and 18 months of Palforzia maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both ARC003 and the open-label, follow-on ARC004 study.

The data from ARC003 and its follow-on study ARC004 indicate that during continued maintenance therapy, the modulation of immunologic responses to treatment continues as demonstrated by a further decrease in peanut-specific IgE, a further increase in peanut-specific IgG4, and a reduction in skin prick test mean wheal diameter.

3.3. Uncertainties and limitations about favourable effects

Efficacy data associated with age

Regarding favourable effects, limitations address especially the efficacy data associated with age. Younger individuals seem to have higher efficacy rates than older children/adolescents. As an example, the primary efficacy analysis was repeated for the ITT population age subgroups of 4 to 11 years and 12 to 17 years. In study ARC010, the results were consistent with the overall population although the treatment difference was less for the much smaller age group of 12 to 17 years (35 Palforzia, 13 placebo; 45.7% [95% CI: 28.8, 63.4]; $p = 0.0033$) compared with 4 to 11 years (97 Palforzia, 30 placebo; 62.9% [95% CI: 52.5, 72.5]; $p < 0.0001$). In ARC003, the younger children (4-11yrs) had slightly higher response rates (52.5% vs 46.3%) and slightly more subjects out of the placebo group showed higher tolerance rates. However, the numbers (especially of 12 – 17 year-old-subjects) are small and a distinction in efficacy between age groups cannot be made. In addition, the treatment difference compared to placebo is still clinically relevant in both age group.

In addition, limited data are available in subjects turning 18 years of age while being on treatment with Palforzia. However, it is agreed with the applicant that young adults with peanut allergy who started treatment at age under 18 years should be given the opportunity to decide with their physicians if continuing Palforzia treatment is the right option for them, as no other approved treatment is available. Appropriate warning and instructions for use have been made in the product information in order to ascertain that the safety profile of Palforzia is clinically manageable.

Uncertainties about threshold

The threshold for the primary endpoint in Europe was discussed in scientific advices and was defined as tolerating a single dose of 1000 mg peanut protein with no more than mild symptoms in the exit

DBPCFC. According to the applicant, already tolerating 300 mg peanut protein would be clinically relevant, as most patients react to lower doses. DBPCFC is the gold standard for evaluation of peanut allergy. As several co-factors may impact the severity of reactions in real-life it is not predicting that the same amount could be tolerated each time in real life. Thus, the defined threshold of 1000mg has a good safety margin and was regarded sufficient for clinical relevance

Uncertainties about effect rate in highly allergic subjects

In order to analyse different effect rates between "highly" allergic subjects compared to less allergic ones (characterised by the level of specific IgE, SPT or the reaction level at baseline DBPCFC) descriptive sub-analyses were presented with the day 120 responses. These sub-analyses suggest that children aged 4-11 years, who are less sensitive seem to benefit most. As such, highest responses were seen in children 4-11 years of age with peanut-specific IgE < 66.7kUA/L at baseline showing a response rate of 75.5%; Children 4-11 years of age with reaction at > 3mg in screening DBPFC showed a response rate of 67.5%. However, as these post-hoc analyses may only be considered exploratory, no conclusions can be drawn to guide treatment decision.

Uncertainties about long term efficacy

The 2 main pivotal clinical studies covers a maintenance phase of 3 (ARC010) and 6 months (ARC003) and only 26 patients have been followed for a maximum of 2 years by the latest cut-off date. Therefore, CHMP considers that no recommendation can be made about the duration of treatment beyond 24 months. The effect of stopping treatment on maintenance of clinical efficacy or on disease modification has not been evaluated. Further long-term efficacy (and safety) data with patients who have received as much as 5-year total treatment and a subsequent 1-year follow-up observation are planned to be collected in the long-term follow-on study ARC008 study listed in the RMP.

Quality of life

Treatment with Palforzia resulted in similar quality of life as measured by subject and parent reported scores from baseline to exit. This result is not surprising and reflects what is seen in the literature. A change in quality of life need more time than the study duration where many subjects experienced an improvement in tolerated amount of peanut protein but still were blinded and did not "experience" real life situations. Treatment adherence is very important and starting treatment with Palforzia requires an active participation and a shared-decision making between patients (and families) and the treating physician. Further data on quality of life are expected to be retrieved from follow-on studies.

3.4. Unfavourable effects

Most comment adverse reactions

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

The incidence of adverse reactions was higher during up-dosing (85.7%) than initial dose escalation (45.1%) and maintenance (57.7%). The general observation that more reactions occur especially during initial dose escalation and up-dosing, may also be associated with quality related concerns regarding the potency range of the Palforzia batches / individual capsules and sachets. Therefore, the applicant committed to ascertain that patients during up-dosing are treated with Palforzia from the same batch in the clinic (first dose) and at home (subsequent 13 doses) at each dose level (please refer to the quality assessment).

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

The induction and high incidence of allergic reactions due to daily contact with the allergen was expected, as well as the observation that adverse events were in general higher during up-dosing than initial dose escalation and maintenance. However, it is obvious that patients only on peanut free diet suffer much less from allergic reactions, including anaphylaxis. The long-term maintenance of desensitization and safety will be further assessed in the ongoing ARC008 study.

Up to now, no markers or special patient characteristics are evident which may predict which individual patient would suffer from more severe allergic effect. However, there seem to be an age-dependent effect. Statistical analysis documented that patients aged ⩾12 years consistently shows an association with higher odds for adverse events. The same was true for certain sensitization parameters at baseline. Therefore, the section 4.4 of the SmPC includes that patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment.

Systemic allergic reactions (anaphylactic reactions)

The main safety risks associated with Palforzia treatment are systemic allergic reactions (anaphylactic reactions) which occurred in 15.1% of subjects; including 0.6% during initial dose escalation, 8.7% during up-dosing, and 9.9% during maintenance. Thus, in opposite other adverse reactions, systemic allergic reactions do not seem to decrease over time during maintenance. The majority of subjects who had systemic allergic reactions had reactions of mild or moderate severity. Severe systemic allergic reaction (anaphylaxis) was reported in 10 subjects (1.1% overall), including 4 subjects (0.4%) during up-dosing and 6 (0.8%) during maintenance at 300 mg/day. In total, 1.6% discontinued due to systemic allergic reaction including 0.3% with anaphylaxis. Of the total population, 10.6% of subjects reported a single episode of systemic allergic reaction and 4.6% reported two or more systemic allergic reactions. Existing data suggest an increased risk of systemic allergic reaction for adolescents (21.9%) than for children (≤ 11 years; 11.9%).

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 (e.g. exercise, hot bath or shower, alcohol consumption, fasting, or intake of non-steroidal anti-inflammatory medications, viral infection). Furthermore, non-adherence to daily treatment, also during subsequent years of maintenance, seems to increase the risk of adverse allergic reactions.

Therefore, guidance on management of co-factors and special warning and precautions for use about systemic allergic reactions including anaphylaxis are included in section 4.4 of the SmPC. Anaphylactic reaction (systemic allergic reaction; any severity) is also described and listed in section 4.8 of the SmPC as an adverse reaction with a frequency very common. The package leaflet is updated accordingly. In addition, anaphylaxis/systemic allergic reactions are listed as an important identified risk in the RMP.

Eosinophilic oesophagitis and other gastrointestinal disorders

The second main safety risk associated with Palforzia is eosinophilic oesophagitis. In clinical trials, 12 out of 1,217 subjects were diagnosed with biopsy-confirmed eosinophilic oesophagitis while receiving Palforzia compared with 0 of 443 subjects receiving placebo. After discontinuation of Palforzia, symptomatic improvement was reported in 12 of 12 subjects. In 8 subjects with available follow-up biopsy results, eosinophilic oesophagitis was resolved in 6 subjects and improved in 2 subjects. In addition, quantitatively most common system organ class of adverse events leading to discontinuation

were associated with gastrointestinal disorders / chronic gastrointestinal events (including abdominal pain, nausea, vomiting and others).

For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia), the potential for a diagnosis of eosinophilic oesophagitis should be considered. In patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, gastroesophageal reflux, chest pain, or abdominal pain, treatment must be discontinued and a diagnosis of eosinophilic oesophagitis should be considered.

"A history of, or current, eosinophilic oesophagitis; other eosinophilic gastrointestinal disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); dysphagia" are contraindications to the use of Palforzia. A warning about gastro-intestinal adverse reactions including eosinophilic oesophagitis is also included in section 4.4 of the SmPC to inform about the risk and to provide instructions if patients develop chronic or recurrent gastrointestinal symptoms. Eosinophilic oesophagitis is described and listed in section 4.8 of the SmPC as an adverse reaction with a frequency uncommon. The package leaflet is updated accordingly. In addition, it is listed an important identified risk in the RMP.

Anaphylaxis/systemic allergic reactions and eosinophilic oesophagitis will be followed as additional pharmacovigilance activities in the ongoing open-label extension for maintenance of desensitization and safety study (ARC008). In addition, both risks are reflected in the healthcare professional education materials and patient and parent/caregiver educational materials.

3.5. Uncertainties and limitations about unfavourable effects

Possible rebound after discontinuation of treatment

When Palforzia treatment is discontinued an increased severity of allergic reactions (i.e. rebound) upon exposure to peanut could possibly occur compared with the severity of allergic reactions before or during treatment. The applicant considered that this is very unlikely due to the competitive inhibition by IgG4 of antigen binding to IgE 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 (i.e. rebound) following discontinuation of food OIT at any point during the process.

As there are no data which address a possible rebound effect in patients, who discontinued treatment, CHMP considered that possible rebound effect should be monitored in the follow-on open-label ARC008 study listed in the RMP. In addition, possible rebound effect after discontinuation of treatment is added as an important potential risk in the RMP. Guidance that patients must continue to carry self-injectable adrenaline at all times if treatment with Palforzia is stopped is also added in section 4.2 of the SmPC.

Use during pregnancy

Patients who were pregnant were not treated with Palforzia in the clinical studies. Potential 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. 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. Therefore, a statement that indicate that there are no data on the clinical experience of Palforzia in pregnant women is

included in section 4.6 of the SmPC. A warning that Palforzia should not be initiated during pregnancy is also included in section 4.6 of the SmPC and 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 is included in section 2 of the package leaflet. 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 is also included in section 4.6 of the SmPC. Use during pregnancy is listed as a missing information in the RMP and pregnancy outcomes in pregnant women exposed to Palforzia ascertained by spontaneous reporting will be monitored in a post-marketing pregnancy registry as listed in the RMP.

Impact on long-term immune-mediated reactions

Long-term data on the incidence of immune-mediated reactions such as anaphylactic reactions and eosinophilic esophagitis are available for 104 subjects and 26 subjects who completed 12 and 18 months respectively of Palforzia maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both ARC003 and the open-label, follow-on ARC004 study. The impact on long-term immune-mediated reactions beyond this period are limited. Therefore this safety concerns is listed as missing information in the RMP and the impact on long-term immune-mediated reactions will be further characterised through the open label, longer-term follow-on study (ARC008) 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.

3.6. Effects Table

Table 24 Effects Table for Palforzia (data cut-off: 15 December 2018)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Threshold in DBPCFC	Toleration single dose of at least 1000 mg 4-17 years	Fraction	ARC003 50.3% (95%CI 45.2,55.3) ARC010 58.3% (95%CI 49.4,66.8)	ARC003 2.4% (95%CI 0.8,6.9) ARC010 2.3% (95%CI 0.1,12.3)	Age dependency of efficacy: higher in young children, less in adolescents	Clinical AR
Maximum symptom at exit DBPCFC	Maximum symptom on any dose	Fraction	ARC003 None 37.6% Mild 32.0% Moderate 25.3% Severe 5.1% ARC010 None 35.6% Mild 41.7% Moderate 18.2% Severe 4.5%	ARC003 None 2.4% Mild 28.2% Moderate 58.9% Severe 10.5% ARC010 None 0% Mild 37.2% Moderate 46.5% Severe 16.3%		
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	TEAEs led to study discontinuation (controlled population)		Palforzia IDE/Up-dosing 92 (10.9%) Maintenance ARC003 0 ARC010 0	Placebo IDE/Up-dosing 8 (2.4%) Maintenance ARC003 1.3% ARC010 0	(New) Data from ARC004, Group 1 (former placebo); not integrated in Integrated Safety Population yet: 47 /102 = 46.1% Discontinuation Discontinuation rate is slightly higher in adolescents	Clinical AR and D121 response
	TRAEs Anaphylactic reaction (Integrated Safety population)		Palforzia IDE 6(0.6%) Up-dosing 69 (7.5%) Maintenance 68 (8.8%) Overall 127 (13.5%)	n/a	Anaphylactic reactions stay at around 9% during maintenance; new data from ARC004, Group 1 (former placebo); not integrated in Integrated Safety Population yet: IDE, Up-Dosing 5 (5.0%) Overall 15 (15.0%) Allergic reaction occurred twice as much in adolescents	D121 Response
	Discontinuation (Integrated Population) Median treatment duration		Overall 42.6% 37.7% 4-11yrs 49.6% 12-17yrs 63.6% 18-55yrs 19.9 month 4-11yrs 18.8 month 12-17yrs 12.0 month 18-55yrs	n/a		D181 Response
	Eosinophilic Esophagitis	Cases	Age 4-17 5 /944 (0.5%) (4 x up-dosing 1 x maintenance) + 7 additional EoEs: 1 adult ARC004 4 / 550 ARC008 1 x ARC001 1 x ARC002	none		

Abbreviations: AR: assessment report; CI: confidence interval; DBPCFC: double-blind placebo-controlled food challenge; EoE: eosinophilic esophagitis; IDE: initial dose escalation; TEAE: Treatment emergent adverse events; TRAEs: Treatment related adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

As most peanut allergic patients react to minimal amounts of peanut proteins (according to literature to an median amount of 125 mg (Mirabel study)) tolerating 300 mg might be the minimal threshold in DBPCFC considered a clinically relevant effect as this value is above most labelled traces of peanut protein in pre-packaged food. Tolerating 1000 mg peanut protein will enhance the clinical relevance to an important level as amounts of peanut protein in self-made food may be higher than 300 mg (e.g. baked goods may even contain little pieces of peanut). If the patients react to an unintended peanut intake, it is highly relevant, how severe the allergic symptoms are and if epinephrine is needed to control symptoms. Therefore, decreasing the level of severity of symptoms and need for epinephrine use are very important.

Importance of favourable effects

The most important favourable effect observed is the improvement in toleration of peanut protein with no more than mild symptom at the exit DBPCFC. Slightly above 50% of patients tolerate a single dose of 1000 mg peanut protein, nearly 70% of patients a single dose of 600 mg and about 75% a single dose of 300 mg. Further important favourable effects were the decrease in the maximum severity of symptoms at the exit DBPCFC and the decrease in epinephrine use as rescue medication during the DBPCFC (ARC003 baseline 36,1 % vs. exit 9,5% subjects need epinephrine; ARC010 baseline 20,8% vs. exit 2,8% of subjects need epinephrine).

The evidence of efficacy was considered statistically convincing and there is good concordance among efficacy endpoints.

Importance of unfavourable effects

The most unfavourable effects during OIT are (severe) systemic allergic reactions (including anaphylaxis), which may be life-threatening. During the clinical studies, the risk of anaphylaxis was higher in the Palforzia groups than placebo groups. Patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment. 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. Furthermore, non-adherence to daily treatment, also during subsequent years of maintenance, seems to increase the risk of adverse allergic reactions.

The second most unfavourable effects were the overall high rate of allergic reactions occurring during treatment (especially impacting the gastrointestinal tract including eosinophilic oesophagitis). The induction of allergic reactions due to daily contact with the allergen is expected, as well as the observation that adverse events were in general higher during up-dosing than initial dose escalation and maintenance.

For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia), the potential for a diagnosis of eosinophilic oesophagitis should be considered. In patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, gastroesophageal reflux, chest pain, or abdominal pain, treatment must be discontinued and a diagnosis of eosinophilic oesophagitis should be considered.

In order to reduce the risk of allergic reactions, including anaphylaxis and eosinophilic oesophagitis appropriate warning and guidelines on management of co-factors have been included in the product information. Anaphylaxis/systemic allergic reactions and eosinophilic oesophagitis are listed as an important identified risk in the RMP and will be followed as additional pharmacovigilance activities in the ongoing open-label extension for maintenance of desensitization and safety study (ARC008). In addition, both risks are reflected in the healthcare professional education materials and patient and parent/caregiver educational materials. This was considered acceptable to the CHMP.

3.7.2. Balance of benefits and risks

So far, no licensed therapeutic option is available for people with peanut allergy in the EU. Current standard of care includes strict avoidance of peanut and education of the patient and family on the recognition and management of allergy symptoms and appropriate use of rescue medications (e.g., antihistamines, epinephrine auto-injectors). The goal of continuous Palforzia treatment in a regimented OIT protocol is to induce and maintain a state of desensitization to peanut protein that is sufficient to reduce the incidence and severity of allergic reactions, including anaphylaxis, in patients with peanut allergy after exposure to peanut.

A favorable treatment effect in the indicated age group of 4-17 years of age has been shown by several endpoints, statistically robust and clinically relevant. Patients who keep up the treatment up to and throughout the maintenance phase showed a very convincing increase in their individual threshold of reactivity against peanut protein. Therefore, patients treated with Palforzia may continue the treatment when they become 18 years of age and older. First data – however limited – on quality of life substantiate that this effect is clinically relevant and may reduce stress and anxiety connected with peanut allergy. Efficacy data are currently 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 or on disease modification has not been evaluated. Palforzia should strictly be used in conjunction with a peanut-avoidant diet.

A high risk of allergic reactions – up to anaphylaxis – was observed due to the intake of peanut protein to which the patients are allergic. Thus, according to the current data, allergic reactions due to the intake of Palforzia (and thus exposure to peanut) are more frequent than in the control group staying on strict avoidance of peanut.

However, the CHMP considered that the risks are adequately described in the product information and adequate risk minimisation measures / additional pharmacovigilance activities are included in the RMP. Long-term data on the maintenance of desensitization and safety will be further assessed in the open-label extension study ARC008. The study will also monitor the safety concerns of anaphylaxis/systemic allergic reactions, eosinophilic oesophagitis, possible rebound after discontinuation of treatment and impact on long-term immune-mediated reactions.

Therefore, CHMP considered that the favorable effects observed in the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy and in the continuation of treatment in patients turning 18 years during treatment outweigh the unfavorable effects.

3.8. Conclusions

The overall B/R of Palforzia is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Palforzia is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

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 4–6, 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

New Active Substance Status

Based on the review of the available data, the CHMP considers that defatted powder of *Arachis hypogaea* L., semen (peanuts), which have some differences in molecular structure, nature of the source material or manufacturing process, does not differ significantly in properties with regard to safety and/or efficacy from previously authorised medicinal products within the European Union and therefore is not considered to be a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0114/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.