14 November 2024
EMA/556850/2024
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/II/0014/G

Note

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

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Table of contents

1. Background information on the procedure....5
1.1. Type II group of variations....5
1.2. Steps taken for the assessment of the product....6
2. Scientific discussion....7
2.1. Introduction....7
2.1.1. Problem statement....7
2.1.2. About the product....9
2.1.3. The development programme/compliance with CHMP guidance/scientific advice....10
2.1.4. General comments on compliance with GCP....10
2.2. Non-clinical aspects....10
2.2.1. Ecotoxicity/environmental risk assessment....10
2.2.2. Discussion on non-clinical aspects....10
2.2.3. Conclusion on the non-clinical aspects....11
2.3. Clinical aspects....11
2.3.1. Introduction....11
2.3.2. Pharmacokinetics....13
2.3.3. Pharmacodynamics....13
2.3.4. Discussion on clinical pharmacology....14
2.3.5. Conclusions on clinical pharmacology....14
2.4. Clinical efficacy....14
2.4.1. Dose response study....15
2.4.2. Main study....15
2.4.3. Discussion on clinical efficacy....42
2.4.4. Conclusions on the clinical efficacy....47
2.5. Clinical safety....47
2.5.1. Discussion on clinical safety....71
2.5.2. Conclusions on clinical safety....74
2.5.3. PSUR cycle....74
2.6. Risk management plan....74
2.7. Update of the Product information....78
2.7.1. User consultation....78
2.7.2. Additional monitoring....78
3. Benefit-Risk Balance....79
3.1. Therapeutic Context....79
3.1.1. Disease or condition....79
3.1.2. Available therapies and unmet medical need....79
3.1.3. Main clinical studies....79
3.2. Favourable effects....80
3.3. Uncertainties and limitations about favourable effects....81
3.4. Unfavourable effects....82
3.5. Uncertainties and limitations about unfavourable effects....83
3.6. Effects Table....84
3.7. Benefit-risk assessment and discussion....84

3.7.1. Importance of favourable and unfavourable effects....84
3.7.2. Balance of benefits and risks....85
3.8. Conclusions....85
4. Recommendations....85
5. EPAR changes....86

List of abbreviations

Abbreviation	Definition
AR101	Peanut (Arachis hypogaea) allergens
Ara h x	Where x = 1 to 17, known peanut allergenic proteins
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
EMA	European Medicines Agency
EoE	Eosinophilic esophagitis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Initial Dose Escalation
Ig	Immunoglobulin
ITT	Intent-to-treat
LOAEL	Lowest Observed Adverse Effect Level
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal anti-inflammatory drug
OIT	Oral immunotherapy
PIP	Pediatric investigational plan
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SD	Standard deviation
SPT	Skin Prick Test
SmPC	Summary of Product Characteristics
WBC	White Blood Cell

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Aimmune Therapeutics Ireland Limited submitted to the European Medicines Agency on 29 August 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	Annex A

Grouped variation consisting of:

C.I.6.a (Extension of indication): Extension of indication to include treatment of patients 1 to 3 years old for PALFORZIA, based on final results from study ARC005; this is a Phase 3 randomized, double-blind, placebo-controlled Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON) to evaluate the safety and efficacy of peanut powder in terms of superiority of placebo in children of 1 year to less than 4 years of age with peanut allergy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The Package Leaflet and Labelling were updated accordingly. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to update the list of local representatives in the Package Leaflet. As part of the application the MAH is requesting a 1-year extension of the market protection.

B.II.e.5.a: Introduction of a new pack-size of 16 capsules of 1 mg (Level 0) in blisters for PALFORZIA, 1 mg, oral powder in capsules for opening.
Due to the lack of a suitable pack-size for the up-dosing phase for patients 1 to 3 years old, a new pack size Level 0 for the up-dosing phase will be introduced. Consequently modules 3.2.P.1 and 3.2.P.7 were updated. Labeling was updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update module 3.2.P.3.1 to take out the EU importation site (editorial change).

The group of variations requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0103/2023) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0103/2023) was completed.

The PDCO issued an opinion on compliance for the PIP (P/0103/2023).

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 MAH 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	29 August 2023
Start of procedure:	16 September 2023
CHMP Rapporteur Assessment Report	10 November 2023
PRAC Rapporteur Assessment Report	16 November 2023
PRAC members comments	22 November 2023
Updated PRAC Rapporteur Assessment Report	23 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	4 December 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2023
Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	30 April 2024
PRAC Rapporteur Assessment Report	3 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	17 May 2024
Updated CHMP Rapporteur Assessment Report	23 May 2024
2nd Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	26 August 2024

Timetable	Actual dates
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	12 August 2024
3rd Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	30 October 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	7 November 2024
Opinion	14 November 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Immunoglobulin E (IgE)-mediated peanut allergy is a food allergy which often begins early in life. It is a potentially serious condition that disproportionately affects children and is associated with severe allergic reactions, including life-threatening anaphylaxis and death.

State the claimed the therapeutic indication

This submission proposes to extend the indication for Palforzia to include treatment of patients 1 to 3 years old. The claimed indication is as follows:

Palforzia is indicated for the treatment of patients aged 1 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older.

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

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 (Nwaru, 2014).

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 (Skolnick, 2001).

Peanut and tree nut allergies account for the majority of fatal food-induced anaphylaxis (Sampson, 2005).

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 (Simons, 2011). However, the severity of an allergic reaction after food allergen exposure is not predictable based on any prior reactions or any specific diagnostic marker (Brough 2015).

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

Aetiology and pathogenesis

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

The manifestation of IgE mediated peanut allergy often occurs already in infancy. In most patients, peanut allergy is lifelong. Some studies have reported that approximately 20% of children diagnosed with peanut allergy outgrow it (Ho, 2008; Fleischer, 2003; Skolnick, 2001). Another study confirmed peanut allergy by food challenge in patients aged 1 year and reported its resolution in 22% of patients by age 4 years (Peters, 2015). In patients who become tolerant to peanut, resolution usually occurs by age 6 years and at a much lower frequency after age 10 years (Bégin, 2013).

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

Diagnosing food allergy (peanut allergy) is challenging. Although molecular diagnostics have shown to help, the gold standard remains the oral food challenge.

The diagnosis of peanut allergy carries medical and emotional significance for the patient. Peanut allergy is the most common cause of anaphylaxis and death related to food allergy in children (Parlaman, 2016; Sampson, 2005; Bock, 2001). A systematic review and meta-analysis of fatal food induced anaphylaxis estimated an incidence rate of 0.73 to 4.25 per million-person years (Umasunthar, 2013).

Unintended food allergen exposures are common, with 55% of patients with peanut allergy reporting at least 1 allergic reaction over approximately 5 years (Sicherer, 1998). Allergic responses may be triggered by minute quantities (< 5 mg) of peanut protein in individuals with peanut allergy (Deschildre, 2016). Factors associated with life threatening allergic reactions to peanut include a history of anaphylaxis to peanut, comorbid conditions (eg, asthma, cardiovascular disease, systemic mastocytosis), the presence of a medical event such as intercurrent illness (eg, viral infection), or cofactors that may decrease the threshold for allergic reaction following allergen exposure (eg, menstruation, stress, fatigue, sleep deprivation, exercise, increased body temperature, intake of NSAIDs, and alcohol use) (Muñoz Cano, 2017).

Management

The standard of care for the management of peanut allergy has primarily been strict peanut avoidance and timely administration of rescue medications in case of an allergic reaction upon exposure (Vickery, 2019). 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 (eg, antihistamines, epinephrine auto injectors). Prompt treatment with intramuscular epinephrine is the first line treatment for anaphylaxis (Muraro, 2007). 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 (Grabenhenrich, 2018).

To follow a strict peanut avoidant diet, can be difficult, and imposes a significant negative quality of life burden on the patient and the patient's family (Anagnostou, 2014; Flokstra de Blok, 2010; Avery, 2003; Primeau, 2000).

Palforzia is approved for patients from 4 to 17 years with a confirmed diagnosis of peanut allergy. So far, no pharmaceutical product is approved for desensitising patients with peanut allergy aged 1 to 3 years old. Therefore, a significant unmet medical need remains for an effective treatment for peanut allergy in children in this age group.

A cure for food allergy remains elusive, although advances continue to be made in understanding its causes and the mechanisms underlying tolerance development.

2.1.2. About the product

The MAH developed AR101 (brand name Palforzia) using a characterised oral immunotherapy (OIT) desensitisation approach for patients with peanut allergy.

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-specific immunotherapy (SIT) is a variously-studied approach, where increasing amounts of an allergen are administered to patients with IgE-mediated allergy to raise the threshold and decrease the severity, including anaphylaxis, of allergic responses to the allergenic agents. An oral route of administration of (especially food) allergens is called OIT.

AR101, characterized peanut (Arachis hypogaea) allergens, is used in a regimented OIT protocol, that consists of daily administration of gradually increasing doses of peanut protein (AR101) until a target daily dose does not induce allergic symptoms. The AR101 dosing regimen is administered in 3 sequential periods: initial dose escalation, up dosing, and maintenance.

The AR101 drug substance (peanut [Arachis hypogaea] allergens) is sourced from raw shelled peanuts that are processed into food-grade, light roast, 12% defatted peanut flour. The drug substance contains approximately 50% peanut protein (w/w). The remaining components include primarily fats, carbohydrates, minerals, and moisture. The active ingredient of AR101 contains allergenic peanut proteins, 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).

AR101 was approved in North America on 31 Jan 2020, in Europe on 17 Dec 2020 (launched in Germany and Austria) and in Switzerland and the UK on 04 May 2021. AR101 is licensed as OIT for children 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. AR101 is also approved as maintenance of efficacy in patients with peanut allergy who turned age 18 years during therapy.

AR101 is not intended for the immediate relief of peanut allergy symptoms and should be used in conjunction with a peanut avoidant diet.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Since the approval of Palforzia in children aged 4 to 17 years, a clinical trial has been conducted in toddlers aged 1 to 3 years with peanut allergy (ARC005 study was conducted in toddlers aged 1 to < 4 years but is referred to as 1 to 3 years interchangeably throughout this document to align with the presentation of age groups in the label and expanding the indication to cover ages 1 to 17 years). This submission presents data from this younger group of patients to support extending the label from children aged 4 to 17 to children and toddlers aged 1 to 17 years.

Referring to the agreed PIP six clinical studies were performed and the PIP is completed.

Positive PDCO opinion has been received for the full compliance check - Positive Opinion (P/0103/2023, EMA/PDCO/139502/2023) of the Paediatric committee on Full PIP Compliance with Paediatric Investigation Plan EMEA-C1-001734-PIP01-14-M06, issued 23 June 2023.

2.1.4. General comments on compliance with GCP

The MH states that the design, conduct, and analyses of the clinical studies in the AR101 program are based on current research approaches, input from European regulatory authorities and the United States Food and Drug Administration (FDA), and compliance with GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance, a natural substance, consists of components of peanut flour which are standard human dietary constituents. Therefore, Palforzia is not expected to pose any risk to the environment even if the environmental entry can be expected to increase due to the filed Type II variation. Dedicated environmental risk assessment (ERA) studies are not considered necessary. The previously obtained waiver for the conduct of environmental studies for Palforzia remains applicable or the current Type II variation. The submitted expert statement is acceptable.

2.2.2. Discussion on non-clinical aspects

Like the initial MAA, also the current Type II variation does not include any toxicology or pharmacology studies. It was and still 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. Palforzia is dosed in relatively small quantities and is administered via the same route as orally ingested, peanut-containing products. Furthermore, there is no need to conduct a specific juvenile animal study in view of the existing clinical experience in children with peanut OIT as well as the limited value of mouse models of human food allergy.

2.2.3. Conclusion on the non-clinical aspects

Palforzia is not expected to pose a risk to the environment.

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

2.3. Clinical aspects

With reference to the initial MAA EMEA/H/C/004917, the clinical development program in children, adolescents, and adults with peanut allergy includes:

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

To date, all studies including ARC008 are now completed.

Study ARC005 is the only study, which addresses children in the age of 1 to 3 years. The results of ARC005 provide the pivotal data to support extending the age of patients treated with AR101 from 4 to 17 years to 1 to 17 years.

2.3.1. Introduction

GCP

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

The MAH 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 1: Tabular overview of clinical studies

Study Identifier [1]	Status, Location No. of Subjects [2]	Study Design	Ages	Primary Outcome Measure
AR101 studies that supported the initial indication for 4 to 17 years				
ARC001 NCT01987817	Completed US Enrolled: 56 Completed: 49	Phase 2, randomized, double-blind, placebo-controlled Maintenance: 2 weeks	4-26 years	Efficacy: Proportion of subjects who achieve desensitization (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

Study Identifier [1]	Status, Location No. of Subjects [2]	Study Design	Ages	Primary Outcome Measure
ARC003 NCT02635776 2015-004257-41	Completed CA, Europe, US Enrolled: 555 Completed: 442	Phase 3, randomized, double-blind, placebo-controlled Maintenance: ~6 months	4-55 years	Efficacy: Proportion of subjects aged 4-17 years who achieve desensitization (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	Completed CA, Europe, US Group 2, cohort 1 Enrolled: 388 Completed: 280	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: 505 Completed: 418	Phase 3, randomized, 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	Completed CA, Europe, US Enrolled: 911 Completed: 0	Open-label follow-on for designated current and future AR101 studies Maintenance: varies	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, randomized, double-blind, placebo-controlled Maintenance: ~3 months	4-17 years	Efficacy: Proportion of subjects who achieve desensitization (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	Completed CA, US Enrolled: 243 Completed: 222	Phase 3 open-label maintenance for ARC007 (AR101-treated) Maintenance: ~6 months	Per prior study	Safety: Frequency of treatment-emergent adverse events including serious adverse events during the overall study period

Study Identifier [1]	Status, Location No. of Subjects [2]	Study Design	Ages	Primary Outcome Measure
AR101 studies in ages 1 to 3 years and expanding the indication for 1 to 17 years				
ARC005 NCT03736447 2018-001749-15	Completed Europe, US Enrolled [3]: 146 Completed: 128	Phase 3, randomized, double-blind, placebo-controlled Maintenance: ~3-6 months	1 to < 4 years [4]	Efficacy: Single highest tolerated dose of at least 1000 mg peanut protein with no more than mild symptoms in the exit DBPCFC

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

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

[3] First subject was randomised in December 2018.

[4] Referred to as 1 to 3 years throughout this document to match the proposed indication in the label.

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

2.3.2. Pharmacokinetics

AR101 is a purified food-derived product which is given orally in small amounts via the same route of administration as normal consumption of food (e.g. peanuts). Components of peanut flour are in general standard human dietary constituents. AR101 drug substance (peanut [Arachis hypogaea] allergens) is sourced from raw shelled peanuts that are processed into food-grade, light roast, 12% defatted peanut flour. The drug substance contains approximately 50% peanut protein (w/w). The remaining components include primarily fats, carbohydrates, minerals, and moisture.

The AR101 development program does not include any formal clinical pharmacology, pharmacokinetic, drug-drug interaction, or food interaction studies, as none of these studies are applicable for the process of OIT. The MAH refers to the CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease (CHMP/EWP/18504/2006), systemic levels of AR101 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 (Berin, 2013).

2.3.3. Pharmacodynamics

Mechanism of action

Peanut allergen specific OIT is a process of desensitisation to peanut for patients with IgE mediated peanut allergy that consists of daily administration of gradually increasing doses of peanut protein until a target daily dose is tolerated. The purpose is to protect patients with peanut allergy from severe systemic allergic reactions by ultimately modifying the patient's immunologic response to peanut.

The precise mechanism of action underlying peanut desensitisation induced by AR101 immunotherapy is not fully understood. However, described immunologic changes in line with a "successful" desensitisation, include increases in allergen-specific IgG4, decreases in allergen-specific IgE, changes of wheal-size following skin prick test (SPT), 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 company's development program go in line with current hypothesis of specific immunomodulatory responses in SIT respectively OIT.

As such, changes in key immunologic markers in the intent to treat (ITT) population (ages 4-17 years) during pivotal phase 3 studies of AR101 (ARC003, ARC010) suggest immunomodulation of peanut allergy within the first year of AR101 treatment, including maintenance treatment of approximately 3 months (ARC010) and 6 months (ARC003).

The MAH describes similar results in toddlers aged from 1 to 3 years in study ARC005. Subjects in the AR101 group had a significant decrease in peanut-specific IgE from screening to exit DBPCFC, while subjects in the placebo group had an increase in peanut-specific IgE; the geometric LS mean ratio (AR101/placebo) was 0.34 (95% CI: 0.24, 0.48 [p-value < 0.0001]).

Primary and secondary pharmacology

No primary or secondary pharmacology were conducted.

2.3.4. 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 mechanism by which OIT desensitises peanut-allergic patients has not been definitely characterised. However, described immunologic changes in line with a "successful" desensitisation upon OIT (or SIT), include increases in allergen-specific IgG4, decreases in allergen-specific IgE and the allergen-specific IgE/IgG4 ratio, increases in allergen-specific regulatory T cell populations, and others. The mode of action including presented data on correspondent trials within the company's development program go in line with current hypothesis of immunomodulatory responses in SIT respectively OIT.

In line with the initial marketing authorisation application, no pharmacokinetics nor pharmacodynamics studies were conducted with Palforzia, and it is agreed. 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.

2.3.5. Conclusions 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.

2.4. Clinical efficacy

Study ARC005 is the only study, which covers children in the age of 1 to 3 years and provides the pivotal data aiming to extending the age of patients treated with AR101 from 4 to 17 years to 1 to 17 years. Thus, this study represents the basis for the current application and is presented in detail in this assessment report.

Study ARC005 was conducted in accordance with the paediatric investigational plan (PIP).

2.4.1. Dose response study

No new dose response studies have been performed.

The escalation, up-dosing, and maintenance doses for toddlers aged 1 to 3 years in study ARC005 were selected based on results of all the previous AR101 studies and on published clinical studies. Dosing was modified to allow for starting up-dosing with a lower dose of 1 mg, and gradually up-dosing to 300 mg compared to all the other studies for 4 years of age and above where the starting dose of the up-dosing was 3 mg and up-dosing was similarly to 300 mg.

2.4.2. Main study

Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (POSEIDON) - Pivotal Phase 3 Study ARC005 in Toddlers Aged 1 to 3 Years

Methods

Study ARC005 was a phase 3 randomised, double-blind, placebo-controlled multicentre study of the efficacy and safety of AR101 in peanut-allergic toddlers aged 1 to 3 years conducted at 14 study sites in North America and 9 in Europe. Eligible subjects who developed age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC were randomly assigned 2:1 to AR101 or placebo.

Dosing and Study Schema

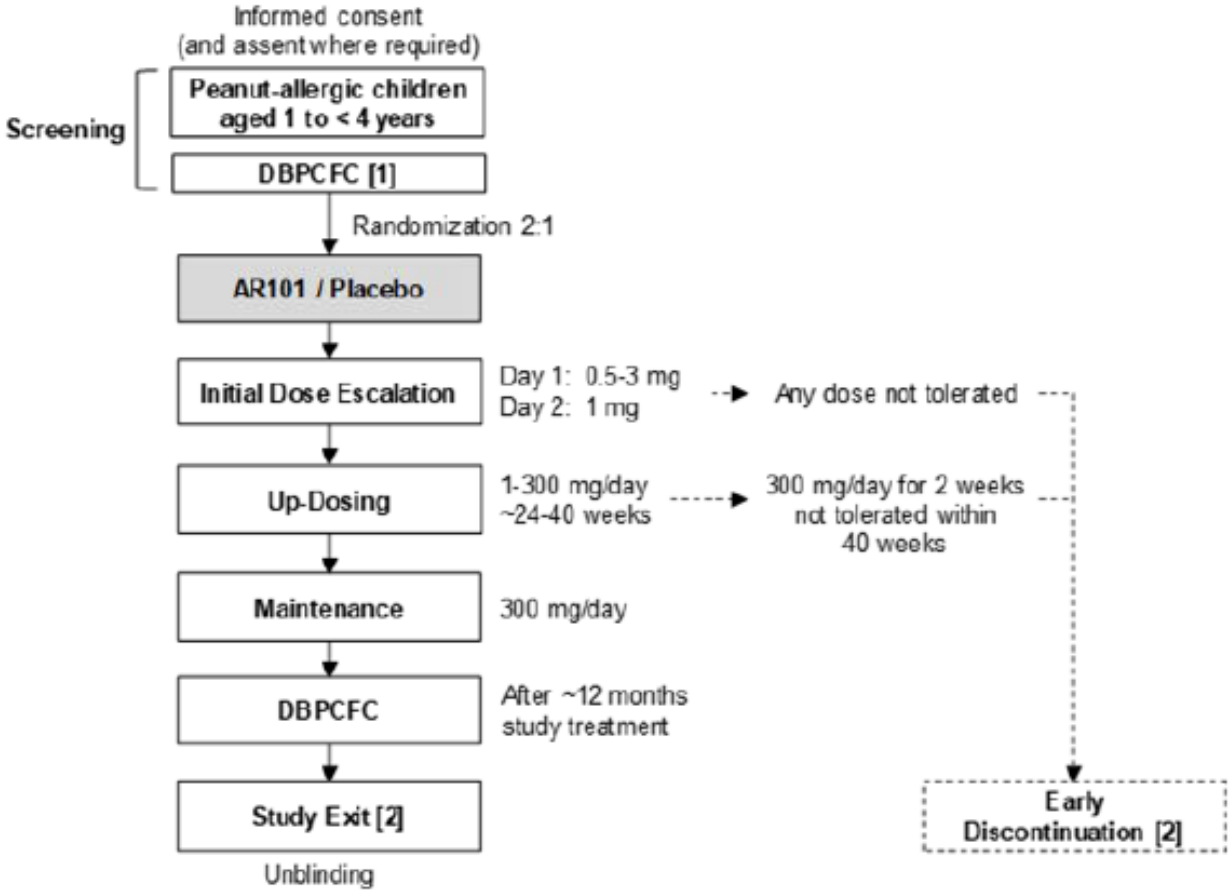
The dosing regimen used in this study was almost the same as for study ARC003, differing only in that tolerability was assessed by initial dose escalation of 0.5, 1, 1.5, and 3 mg on Day 1 (omitting the 6 mg dose used in the other phase 3 studies), administered at 20- to 30-minute intervals, with an additional single 1 mg dose on Day 2 (instead of a single 3 mg dose used in the other phase 3 studies). Subjects who tolerated the 3 mg dose on day 1 returned on day 2 for a single 1 mg dose. Subjects who tolerated the 1 mg dose with no more than mild allergy symptoms that were not dose-limiting began the up-dosing period. Subjects who did not tolerate any dose on day 1 or day 2 discontinued.

The up-dosing period was approximately 6 months (maximum 40 weeks), with dose escalation approximately every 2 weeks. Daily doses of study product during up-dosing were 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of study product at each new level was administered under medical supervision at the study site; the remaining doses at each dose level were administered daily at home as tolerated. Dose adjustments could be allowed. Subjects who tolerated the 300 mg/day dose for 2 weeks within 40 weeks began the maintenance period. Subjects who were unable to tolerate the 300 mg/day dose for 2 weeks within 40 weeks of up-dosing discontinued early from the study.

Subjects who began maintenance treatment continued daily dosing with study product at 300 mg/day for an overall total of approximately 12 months of treatment, with study site visits every 4 weeks. The duration of maintenance treatment could vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks). Dose adjustments could be allowed.

After a total of approximately 1 year of blinded treatment, subjects completed an exit DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative). This “new” top single-

dose of 2000 mg single dose selected for the exit DBPCFC was based on recent study results of in peanut allergic children (Bird, 2017; Du Toit, 2015; Jones, 2022; Vickery, 2017).



[1] Eligible subjects had age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in the screening DBPCFC.
[2] Subjects with unresolved adverse events or who had gastrointestinal adverse events of interest had safety follow-up.
DBPCFC, double-blind, placebo-controlled food challenge.

Figure 1: Schema of study design (ARC005)

Study participants

Similar to the studies in children aged 4 to 17 years and older, toddlers aged 1 to 3 years were required to have a screening DBPCFC to identify appropriate subjects with dose-limiting symptoms.

Table 2: Study design comparison between studies ARC003, ARC010, ARC005

Study Design Element	ARC003	ARC010	ARC005
Location	US, Canada, Europe (UK, Ireland, Germany, Spain, Italy, Sweden, Denmark, Netherlands)	Europe: UK, Ireland, Germany, Spain, Italy, Sweden, France	Europe and North America
Age group	4-55 years	4-17 years	1 to 3 years
Inclusion DBPCFC	Sensitive to 100 mg or less peanut protein	Sensitive to 300 mg or less peanut protein	Sensitive to 300 mg or less peanut protein

Main inclusion criteria

- Subjects were to be aged between 1 to < 4 years at randomisation.
- Subjects were to have a sensitivity to peanut, defined as: no known history of peanut ingestion and serum IgE to peanut of ≥ 5 kUA/L within the 12 months before randomisation; or a documented history of peanut allergy and a mean wheal diameter on skin prick test to peanut of at least 3 mm greater than the negative control (diluent) or serum IgE to peanut of ≥ 0.35 kUA/L within the 12 months before randomisation.
- Subjects were to have age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein of > 3 mg to ≤ 300 mg in a screening DBPCFC.

Main exclusion criteria

- History of severe or life-threatening anaphylaxis or anaphylactic shock.
- History of biopsy-confirmed diagnosis of Eosinophilic esophagitis (EoE); other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); or symptoms of dysphagia (eg, difficulty swallowing, food “getting stuck”).
- History of a mast cell disorder including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (eg, cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema.
- Moderate or severe asthma or mild asthma that was uncontrolled/difficult to control.
- Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector.
- History of food protein-induced enterocolitis syndrome (FPIES) within 12 months before screening.
- History of failure to thrive or any other form of abnormal growth, or developmental or speech delay that precludes age-appropriate communication.

Treatments

The AR101 active pharmaceutical ingredient was initially sourced as raw peanuts, *Arachis hypogaea*. The AR101 drug product was formulated with bulking and flow agents in graduated doses, encapsulated in hydroxypropyl methyl cellulose (HPMC) or filled in foil-laminate sachets and supplied in color-coded pull-apart capsules at 5 dosage strengths and sachets. The corresponding color-matched placebo (AR101-placebo) consisted of excipients filled in matching capsules or sachets.

The first dose at each new dose level and the first dose of each kit issued during maintenance was administered at the study site under medical supervision.

Procedures for preparation and administration were the same at the study site or at home. Capsules or sachets containing AR101 or placebo were emptied into and mixed with a vehicle food (eg, applesauce, yogurt, pudding, or other age-appropriate semisolid matrix food). 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. The product was to be consumed as promptly after mixing as practicable and as part of a meal for dosing at home. Study product could be stored for up to 24 hours under conditions appropriate for the food matrix in which it was prepared. For delays longer than 24 hours, the product was to be discarded and a new study product dose mixed and consumed. It was recommended that 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.

Objectives

Primary objective

- Efficacy of AR101 treatment in peanut-allergic subjects aged 1 to < 4 years, assessed by tolerability of specified doses of peanut protein in a DBPCFC.

Secondary objective

- Safety and tolerability of study treatment;
- Efficacy of AR101, assessed by tolerability of other specified single doses of peanut protein in a DBPCFC;
- Maximum severity of allergy symptoms in a DBPCFC.

Outcomes/endpoints

The primary and secondary endpoints for Europe and North America specified for this study are presented below; data presented in the rest of this document relate to endpoints as specified for Europe.

Primary endpoint

Europe - The proportion of subjects who tolerated a single dose of at least 1000 mg peanut protein with no more than mild symptoms at the exit DBPCFC.

North America - The proportion of subjects who tolerated a single dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC.

Secondary endpoint

If the primary efficacy endpoint analysis was significant at the 0.05 level, key secondary efficacy endpoints were evaluated in hierarchical order as follows:

Europe

1. 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;
2. 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;

3. The maximum severity of symptoms that occurred at any challenge dose of peanut protein during the exit DBPCFC.

North America

1. 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;
2. Desensitisation response rate at a single dose of 1000 mg peanut protein: 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;
3. The maximum severity of symptoms that occurred at any challenge dose of peanut protein during the exit DBPCFC.

Exploratory endpoint

- Change from baseline in peanut-specific and peanut component-specific IgE and IgG4;
- Change from baseline in mean wheal diameter and mean erythema diameter on skin prick test to peanut;
- Change from baseline in the Test for Respiratory and Asthma Control in Kids and Eczema Area and Severity Index scores;
- Palatability of study product;
- Proportion of subjects who tolerated a single highest dose of 2000 mg peanut protein (4043 mg cumulative) during the exit DBPCFC;
- Change in baseline in the single highest tolerated dose of peanut protein at the exit DBPCFC;
- Maximum dose of peanut protein reached with no more than mild allergy symptoms at the exit DBPCFC.

Sample size

The sample size of this study (approximately 132 subjects randomly assigned 2:1 to AR101 or placebo) was selected to provide sufficient power to detect a treatment difference for the primary efficacy analysis for each major health authority region (North America estimand and Europe estimand).

For North America estimand, the sample size provides 85% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo with an at least 15% margin for the primary efficacy endpoint of the proportion of subjects tolerating an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. Calculations are based on the Farrington and Manning method (Farrington, 1990) for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the DBPCFC of 55% in AR101-treated subjects, and a maximum desensitisation rate of 15% in placebo-treated subjects, conducted in the ITT population.

For Europe estimand, the sample size provides > 95% power to demonstrate a significantly higher desensitisation response rate with AR101 compared with placebo for the primary efficacy endpoint of

the proportion of subjects tolerating an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations are based on the Farrington and Manning method for the difference in proportions and assume a type I error of 0.05, 2-sided test, a desensitization rate based on the DBPCFC of 50% in AR101-treated subjects, and a maximum desensitization rate of 10% in placebo-treated subjects, conducted in the ITT population.

The desensitisation rates used in the sample size calculations account for an estimated 25% of subjects across both treatment groups to drop out or discontinue early from the study; these subjects will not be replaced and will be considered non responders.

Randomisation

Randomisation was performed using an interactive response system on day 1 of initial dose escalation.

Randomisation was central and treatment allocation was 2:1 (AR101 or placebo). Randomisation was stratified by region (North America, Europe); at least 30% of subjects were enrolled in Europe.

Blinding (masking)

This was a double-blind study. Study treatments and immunology laboratory results obtained after screening were blinded. All subjects, study site personnel (including investigators), and sponsor staff and its representatives were blinded to treatment identity, except the designated unblinded person who will access the interactive response system to obtain the randomisation order for the peanut protein and placebo challenge days, and prepare the DBPCFC material.

The peanut and placebo food challenges were conducted in a double-blind manner using food challenge material provided by an unblinded study site pharmacist, nutritionist, or study coordinator. Subjects, investigators, study site personnel, and sponsor personnel involved in the conduct of the study were blinded to treatment assignment during the treatment periods (initial dose escalation, up-dosing, and maintenance) through completion of the exit DBPCFC and after all major data queries for the subject were resolved. Unless required for safety reasons (eg, medical treatment of serious adverse events), subjects eligible for an exit DBPCFC were not unblinded to their treatment assignment before the DBPCFC.

Statistical methods

Analysis populations

The intention-to-treat (ITT) population (ie, full analysis set) was defined as all subjects who receive any part of 1 dose of study product. The ITT population was planned to be used for all efficacy analyses unless otherwise specified, and analysed according to randomised treatment. If no subjects receive the incorrect treatment, the ITT population was expected to be the same as the safety population.

The completer population was defined as all subjects in the ITT population who complete study treatment and have an evaluable exit DBPCFC (completion of at least the peanut food challenge day).

The per protocol population was then planned to include all subjects in the completer population who have no major protocol deviations that may influence the desensitization response.

The safety population was planned to be defined as all subjects who receive any randomized study treatment (ie, who receive any part of 1 dose of study product and complete 1 study visit).

The safety population was to be used for all safety analyses and analysed according to treatment received.

Analysis methods

The ITT population and Farrington-Manning test were planned to be used for these analyses. Subjects tolerating a single dose of at least 600 mg peanut protein for North America and at least 1000 mg peanut protein for Europe were planned be considered responders; subjects who do not tolerate a single dose of at least 600 mg peanut protein for North America and at least 1000 mg peanut protein for Europe were planned to be considered nonresponders. Nonresponders were planned to also include subjects who withdraw consent or discontinue early anytime before the exit DBPCFC.

Desensitisation response rates and associated 95% CIs were planned to be presented for each treatment group using exact Clopper-Pearson CIs. The 95% CI for the treatment difference (desensitisation rate for AR101 treatment minus desensitization rate for placebo) was planned to be based on the Farrington-Manning method. The primary efficacy endpoint for North America was planned to be considered met if the lower bound of the 95% CI is greater than the prespecified margin of 0.15. The primary efficacy endpoint for Europe was to be considered met if the lower bound of the 95% CI is greater than 0.

Secondary analyses

Secondary efficacy endpoints were planned to be assessed in hierarchical order by major health authority region (North America and Europe) if the primary efficacy endpoint analysis is significant at the 0.05 level. Each endpoint was planned to be evaluated for statistical significance (2-sided, $p < 0.05$) only if all preceding in the hierarchy and the primary analysis of the primary efficacy endpoint are statistically significant in favour of AR101.

Europe:

1. The proportion of subjects who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC was planned to be assessed using the ITT population and Farrington-Manning test.
2. The proportion of subjects who tolerate an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC was planned to be assessed using the ITT population and Farrington-Manning test.
3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC was planned to be assessed by tabulating the number and percentage of subjects in the ITT population by maximum severity of allergy symptoms at the exit DBPCFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores (row mean score differences statistic) stratified by geographic region was planned to be used to test for a treatment difference.

Interim analyses

No interim analyses were planned.

Missing data

Missing values for efficacy variables was not planned be replaced or imputed; no interpolation or extrapolation was to be applied to missing values unless otherwise specified in the statistical analysis plan.

Further analyses were conducted ad-hoc (not specified in the protocol):

Sensitivity analyses of the primary efficacy endpoint were performed for the completer population and per protocol population (if sufficiently different from the completer population). 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 AR101-treated subjects were considered nonresponders. Sensitivity analyses were also conducted to assess the potential impact of restrictions due to the COVID-19 pandemic, as the total duration of the study and of study treatment for individual subjects were extended as needed to allow completion of study treatment. The following sensitivity analyses were performed:

- Subgroup analysis including subjects who were on study treatment for up to 64 weeks, corresponding to a maximum allowable duration of up to 40 weeks of up-dosing combined with up to 24 weeks of maintenance, as prespecified per protocol prior to onset of the pandemic.
- Subgroup analysis excluding subjects with more than 24 weeks of maintenance treatment, corresponding to the maximal allowable duration of maintenance therapy prior to the exit DBPCFC as specified per protocol prior to onset of the pandemic.

Results

Participant flow

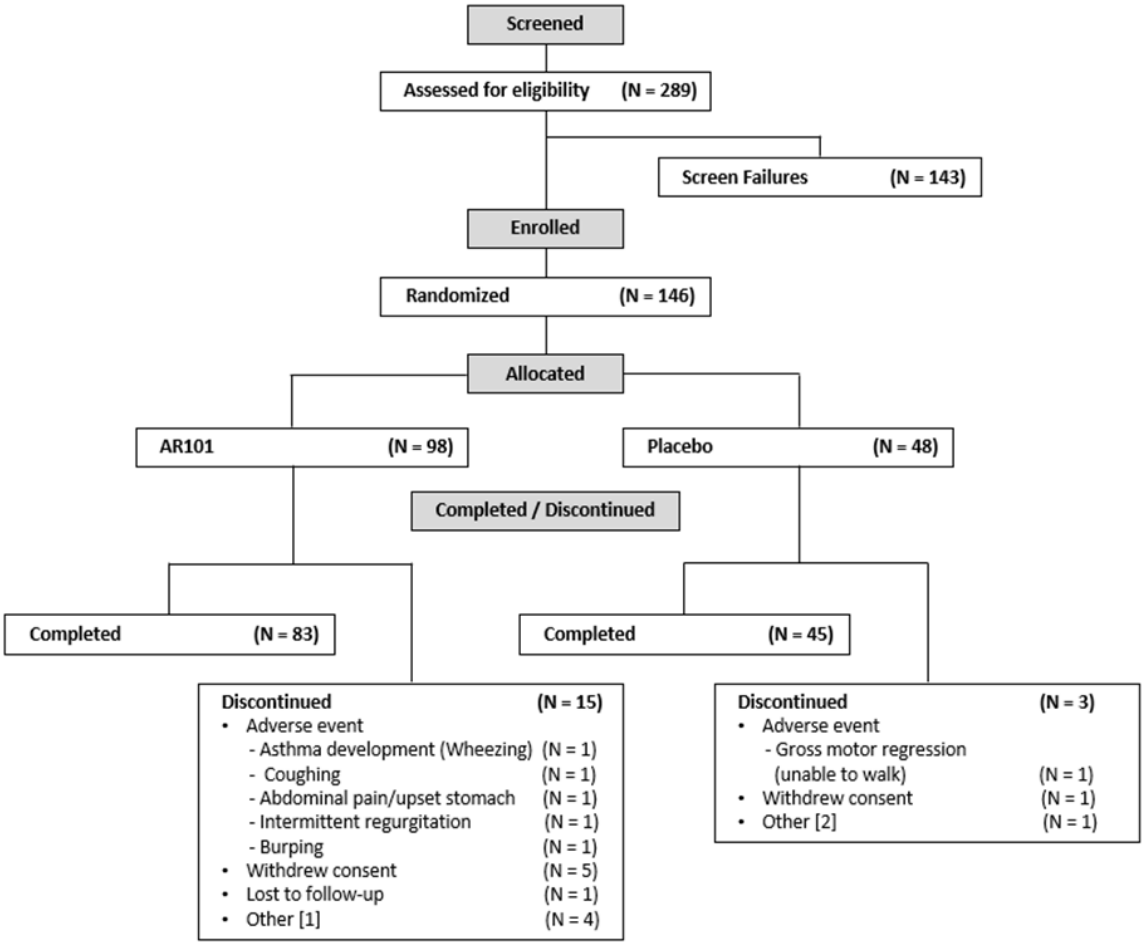


Figure 2: Subject Disposition Flow Chart for Toddler Study ARC005 (All Subjects, 1 to 3 Years)

Similar to the studies in children aged 4 to 17 years, toddlers were required to have a screening DBPCFC to identify appropriate subjects with dose-limiting symptoms. Approximately one-third of the total population tolerated 10 mg or less dose of peanut protein at the screening DBPCFC, and approximately two-thirds had a single highest tolerated dose of peanut protein at the screening DBPCFC of 30 or 100mg.

Of the 146 subjects randomly assigned to study treatment (98 to AR101 and 48 to placebo), 83 of 98 (84.7%) subjects in the AR101 group and 45 of 48 (93.8%) subjects in the placebo group completed the study.

Recruitment

The first subject was screened for this study on 03 November 2018 and the first dose of blinded study product was administered on 27 December 2018. The last subject visit was on 05 July 2022.

Conduct of the study

The study was conducted during the COVID-19 pandemic, which lead to some protocol deviations.

Amendments

The original protocol dated 31 May 2018 had 7 amendments (4 global, and 3 country-specific). Major changes to the global protocol (4) were made to modify the eligibility criteria to ensure that appropriate subjects in the toddler age group were enrolled, the following major changes were consequential to this first amendment.

No changes were made in the planned analysis after its finalisation on 21 Jul 2022.

Protocol Deviations

Major protocol deviations were defined as deviations that could affect subject rights, safety, or well-being; or the integrity of the study data. A total of 37 subjects (25.3%) had 1 or more major protocol deviations (29 subjects [29.6%] AR101, 8 subjects [16.7%] placebo) (Table 3).

The most common deviation category was informed consent (11 subjects, 11.2% AR101 and 4 subjects, 8.3% placebo). This related to obtaining informed consent for revised procedures to the COVID-19 pandemic and was not considered to impact data integrity. An additional category was dosing errors (8 subjects, 8.2% AR101 and 1 subject, 2.1% placebo), of which 5 were overdose and 3 were continuation of study product dosing after study exit. Other common deviation categories were procedures not done per protocol (5 subjects, 5.1% AR101 and 2 subjects, 4.2% placebo), and no blinded assessor for study exit (3 subjects, 3.1% AR101). Two AR101 treated subjects (2.0%) had deviation due to damaged investigational product. One subject in each treatment group had a deviation in treatment compliance (missed doses for > 7 consecutive days or missed doses for ≥ 3 consecutive days on 3 occasions).

By geographic region, deviation categories were similar but more subjects (28 [33.3%]) in North America had major protocol deviations compared with 9 subjects (14.5%) in Europe.

Table 3: Major protocol deviations (safety population)

	AR101 (N = 98)	Placebo (N = 48)	Total (N = 146)
Any major protocol deviations	29 (29.6%)	8 (16.7%)	37 (25.3%)
Deviation category			
Blinded physician perform the exit DBPCFC	1 (1.0%)	0	1 (0.7%)
Damaged IP	2 (2.0%)	0	2 (1.4%)
Delayed study exit visit	1 (1.0%)	0	1 (0.7%)
Dosing errors	8 (8.2%)	1 (2.1%)	9 (6.2%)
Eligibility criteria not met [1]	1 (1.0%)	0	1 (0.7%)
Incorrect order of food challenge material administered on exit DBPCFC days 1 and 2	1 (1.0%)	0	1 (0.7%)
Informed consent	11 (11.2%)	4 (8.3%)	15 (10.3%)
No blinded assessor for exit DBPCFC	0	1 (2.1%)	1 (0.7%)
No blinded assessor for exit visit	3 (3.1%)	0	3 (2.1%)
Potential unblinding	1 (1.0%)	0	1 (0.7%)
Procedure not done per protocol	5 (5.1%)	2 (4.2%)	7 (4.8%)
Treatment compliance	1 (1.0%)	1 (2.1%)	2 (1.4%)

Source: Table 14.1.2.1
Subjects with more than 1 deviation in a category were counted only once and could be included in more than 1 category.
[1] Subject was in observational follow-up of another study and was allowed to enroll in study ARC005 after discussion with the sponsor.
DBPCFC, double-blind, placebo-controlled food challenge.

Baseline data

The demographic and baseline characteristics (including allergy history) for 1 to 3 years olds in the ITT population were similar in the 2 treatment groups (Table 4, Table 5), and are representative of the patient population likely to seek treatment due to their clinical history of reactions to peanut.

Table 4: Demographic characteristics (ITT population, 1 to 3 years)

Characteristic	AR101 (N = 98)	Placebo (N = 48)	Total (N = 146)
Age [1]			
Median	2.0	2.0	2.0
Min, max	1, 3	1, 3	1, 3
Age category			
1 - <2	33 (33.7%)	16 (33.3%)	49 (33.6%)
2 - <3	35 (35.7%)	15 (31.3%)	50 (34.2%)
3 - <4	30 (30.6%)	17 (35.4%)	47 (32.2%)
Sex			
Male	57 (58.2%)	28 (58.3%)	85 (58.2%)
Female	41 (41.8%)	20 (41.7%)	61 (41.8%)
Ethnicity			
Hispanic or Latino	5 (5.1%)	3 (6.3%)	8 (5.5%)
Not Hispanic or Latino	75 (76.5%)	31 (64.6%)	106 (72.6%)
Not collected	18 (18.4%)	14 (29.2%)	32 (21.9%)
Race [2]			
Asian	18 (18.4%)	11 (22.9%)	29 (19.9%)
Black or African American	4 (4.1%)	2 (4.2%)	6 (4.1%)
Native Hawaiian or Other Pacific Islander	0	1 (2.1%)	1 (0.7%)
White	66 (67.3%)	32 (66.7%)	98 (67.1%)
Other	8 (8.2%)	2 (4.2%)	10 (6.8%)
Not collected	4 (4.1%)	4 (8.3%)	8 (5.5%)
Country			
United States	56 (57.1%)	28 (58.3%)	84 (57.5%)
United Kingdom	29 (29.6%)	12 (25.0%)	41 (28.1%)
Germany	9 (9.2%)	5 (10.4%)	14 (9.6%)
France	4 (4.1%)	3 (6.3%)	7 (4.8%)

[1] Calculated relative to the date of informed consent.
[2] Subjects could be included in more than 1 category.
ITT, intent-to-treat; Min, max, minimum, maximum

The single highest tolerated dose of peanut protein at the screening DBPCFC was 30 mg for 32.7% of the AR101 group and 35.4% of the placebo group. About one-third of the total population tolerated 10 mg or less dose of peanut protein at the screening DBPCFC, and about two-thirds had a single highest tolerated dose of peanut protein at the screening DBPCFC of 30 or 100mg. The median single highest tolerated dose was 30 mg in both groups.

Table 5: Select Baseline Characteristics (ITT Population, 1 to 3 Years)

Characteristic	AR101 (N = 98)	Placebo (N = 48)	Total (N = 146)
Single highest tolerated dose of peanut protein at screening DBPCFC			
0.3 mg	0	0	0
1 mg [1]	1 (1.0%)	1 (2.1%)	2 (1.4%)
3 mg	13 (13.3%)	8 (16.7%)	21 (14.4%)
10 mg	17 (17.3%)	10 (20.8%)	27 (18.5%)
30 mg	32 (32.7%)	17 (35.4%)	49 (33.6%)
100 mg	35 (35.7%)	12 (25.0%)	47 (32.2%)
300 mg	0	0	0
History of systemic allergic reaction to peanut [2]			
Yes	36 (36.7%)	17 (35.4%)	53 (36.3%)
No	62 (63.3%)	31 (64.6%)	93 (63.7%)
Nonpeanut allergy history [2]			
Allergic rhinitis	13 (13.3%)	10 (20.8%)	23 (15.8%)
Asthma	8 (8.2%)	4 (8.3%)	12 (8.2%)
Atopic dermatitis	62 (63.3%)	29 (60.4%)	91 (62.3%)
Food allergies other than peanut	71 (72.4%)	33 (68.8%)	104 (71.2%)
Other	18 (18.4%)	6 (12.5%)	24 (16.4%)

[1] Subjects had no dose limiting symptoms at the 3 mg dose and met the protocol inclusion criteria based on dose-limiting symptoms; concurrent medications were given at later doses in the screening DBPCFC.

[2] Subjects could be included in more than 1 category.

CSR, clinical study report; DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat.

Both the baseline median peanut-specific IgE and Ara h 2 IgE were numerically lower in the AR101 group (6.8 kUA/L and 5.190 kUA/L, respectively) compared with the placebo group (30.0 kUA/L and 14.200 kUA/L). The median mean wheal diameter in the screening skin prick test to peanut, was balanced 9.0 mm (range, 4-36 mm) for the AR101 group and 9.75 mm (range, 2-26.5 mm) for the placebo group.

Table 6: Baseline immunology values and skin prick test (ITT Population)

Characteristic	AR101 (N=98)	Placebo (N=48)	Total (N=146)
Total IgE (IU/mL)			
n	86	45	131
Median	162.5	175.0	164.0
Q1, Q3	52.0, 453.0	41.0, 343.0	51.0, 422.0
Min, max	5, 3324	9, 5508	5, 5508
Peanut-specific IgE (kUA/L)			
n	87	45	132
Median	6.800	30.000	10.080
Q1, Q3	2.280, 33.500	2.120, 69.700	2.230, 51.450
Min, max [3]	0.01, 100.00	0.06, 100.00	0.01, 100.00
Peanut-specific IgG4 (mgA/L)			
n	85	45	130
Median	370.0	360.0	360.0
Q1, Q3	120.0, 910.0	100.0, 790.0	110.0, 850.0
Min, max	70, 16900	70, 8880	70, 16900
Peanut-specific IgE/IgG4 ratio			
n	85	45	130
Median	0.019	0.040	0.024
Q1, Q3	0.008, 0.050	0.013, 0.137	0.008, 0.065
Min, max	0.00, 0.32	0.00, 1.43	0.00, 1.43
Skin prick test mean wheal diameter (mm) [2]			
n	95	48	143
Median	9.00	9.75	9.50
Q1, Q3	7.00, 13.50	6.75, 13.00	7.00, 13.00
Min, max	4.0, 36.0	2.0, 26.5	2.0, 36.0
Ara h 2 IgE (kUA/L)			
n	86	45	130
Median	5.190	14.200	6.270
Q1, Q3	1.260, 25.400	1.790, 54.700	1.370, 38.200
Min, max	0.01, 100.00	0.05, 100.00	0.01, 100.00
Ara h 2 IgG4 (mgA/L)			
n	85	45	130
Median	0.070	0.060	0.065
Q1, Q3	0.020, 0.260	0.010, 0.200	0.010, 0.250
Min, max	0.01, 1.71	0.01, 2.44	0.01, 2.44
Ara h 2 IgE/IgG4 ratio			
n	85	45	130
Median	77.519	142.857	105.440
Q1, Q3	21.500, 234.500	43.290, 418.571	25.200, 263.750
Min, max	0.56, 2000.00	4.33, 10000.00	0.56, 10000.00

[1] Values for peanut-specific IgE were capped at 100 kUA/L due to laboratory analysis procedures.

[2] 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; ITT, intent-to-treat; Min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

Numbers analysed

The ITT population for subjects (98 AR101, 100% and 48 placebo, 100%) was used as the primary analysis population for all primary and secondary efficacy endpoints. All subjects received the correct study treatment at randomisation. The ITT and safety populations are the same.

Supportive and sensitivity analyses of the primary efficacy endpoint and key secondary endpoints were performed for subjects using the ITT (98 AR101-treated subjects, 100.0% and 48 placebo-treated subjects, 100.0%) or completer population (83 AR101-treated subjects, 84.7% and 45 placebo-treated subjects, 93.8%). Analyses of the primary and all secondary efficacy endpoints were performed using the PP population if it differed from the completer population by greater than 5% in either treatment group. Sensitivity analyses of selected endpoints were performed if the PP population differed from the completer population by ≥ 5% in both treatment groups. The PP population differs from the completer population by the specified threshold. Therefore, both primary analysis (desensitization response rate) and secondary analyses (eg, maximum severity of symptoms at exit DBPCFC) were calculated for completer and PP populations, in addition to ITT.

Analysis populations by treatment group are summarised in Table 7.

Table 7: Analysis populations by treatment group

	AR101	Placebo	Total
Safety population [1]	98 (100%)	48 (100%)	146 (100%)
ITT population [2]	98 (100%)	48 (100%)	146 (100%)
Completer population [3]	83 (84.7%)	45 (93.8%)	128 (87.7%)
PP population [4]	74 (88.8%)	42 (87.5%)	116 (79.5%)

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

Outcomes and estimation

The primary and all key secondary efficacy endpoints were met for this study. The key secondary efficacy endpoints were evaluated in hierarchical order by major health authority region according to the SAP.

Primary efficacy endpoint

Treatment with AR101 resulted in a statistically significant treatment effect over placebo in the proportion of subjects 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.

Of 98 subjects in the ITT population who received AR101, the desensitisation response rate was 68.4% (95% CI: 58.2, 77.4) compared with 4.2% (95% CI: 0.5, 14.3) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 64.2% (95% CI: 47.0, 81.4); $p < 0.0001$.

For the Completer population, treatment with AR101 resulted in a statistically significant treatment effect over placebo in the proportion of subjects 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.

Of 83 subjects in the Completer population who received AR101, the desensitisation response rate was 80.7% (95% CI: 70.6, 88.6) compared with 4.4% (95% CI: 0.5, 15.1) for 45 subjects who received placebo. The treatment difference (AR101-placebo) was 76.3% (95% CI: 58.2, 94.4); p < 0.0001.

For the PP population, treatment with AR101 resulted in a statistically significant treatment effect over placebo in the proportion of subjects 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.

Of 74 subjects in the PP population who received AR101, the desensitisation response rate was 82.4% (95% CI: 71.8, 90.3) compared with 4.8% (95% CI: 0.6, 16.2) for 42 subjects who received placebo. The treatment difference (AR101-placebo) was 77.7% (95% CI: 58.8, 96.5); p < 0.0001.

Key secondary efficacy endpoints

1. Desensitisation response rate at a single dose of 600 mg peanut protein: The proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC.

Of 98 subjects in the ITT population who received AR101, the desensitisation response rate for the key secondary efficacy endpoint was 73.5% (95% CI: 63.6, 81.9) compared with 6.3% (95% CI: 1.3, 17.2) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 67.2% (95% CI: 50.0, 84.5); p < 0.0001.

2. Desensitisation response rate at a single dose of 300 mg peanut protein: The proportion of subjects who tolerated a single highest dose of at least 300 mg peanut protein with no more than mild symptoms at the exit DBPCFC.

Of 98 subjects in the ITT population who received AR101, the desensitisation response rate for the key secondary efficacy endpoint for Europe was 79.6% (95% CI: 70.3, 87.1) compared with 22.9% (95% CI: 12.0, 37.3) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 56.7% (95% CI: 39.8, 73.5); p < 0.0001.

3. The maximum severity of symptoms that occurred at any challenge dose of peanut protein during the exit DBPCFC.

The maximum severity of symptoms was none for 51.0% of subjects in the AR101 group and 4.2% of subjects in the placebo group. The maximum severity of symptoms was mild for 29.6% and 47.9% of subjects (AR101 and placebo), moderate for 17.3% and 43.8%, and severe for 2.0% and 4.2%. The p-value was < 0.0001 for the treatment difference in maximum severity of symptoms at any challenge dose.

The maximum severity of symptoms was similar between groups at screening: mild for 48.0% AR101 and 43.8% placebo, moderate for 45.9% and 54.2%, and severe for 6.1% and 2.1%. The proportion of subjects with any symptoms during the placebo screening DBPCFC was similar between groups (6.1% AR101, 8.3% placebo), and the maximum severity of any symptoms was none for most of the subjects (93.9% AR101, 91.7% placebo) and mild for few subjects (6.1% AR101, 8.3% placebo).

Exploratory Efficacy Endpoints

- Changes in Peanut-Specific and Peanut Component-Specific Serum Immunoglobulins

The trend in peanut-specific IgE in the AR101 group was a decrease from screening to the exit while in the Placebo group the trend was an increase from screening to exit (Table 8).

In addition, the overall Ara h peanut-specific IgE, IgG4, IgE/IgG4 ratio in the AR101 group was an increase from screening to the early discontinuation and decrease at the exit. The trend in Ara h subtype peanut-specific IgE in the AR101 group was a decrease from screening to the exit, while in the

placebo group the trend was an increase from screening to exit. The changes in Ara h 2 peanut-specific IgE were similar to peanut-specific IgE. The overall trend in Ara h 2 peanut-specific IgG4 in the AR101 group was an increase from screening to the exit DBPCFC.

Table 8: Change From Baseline in Immunoglobulin Values in Toddler Study ARC005 (ITT Population, 1 to 3 Years)

Parameter	Time Point	AR101 (N = 98)	Placebo (N = 48)
ps-IgE (kUA/L)	Screening DBPCFC		
	n	87	45
	Mean (SD)	25.27 (35.495)	38.92 (37.218)
	Geometric mean (SD)	7.04 (6.712)	12.26 (8.429)
	Median	6.80	30.00
	Q1, Q3	2.3, 33.5	2.1, 69.7
	Min, max	0.0, 100.0	0.1, 100.0
	Exit DBPCFC		
	n	76	38
	Mean (SD)	15.20 (24.939)	52.89 (40.310)
	Geometric mean (SD)	3.33 (7.713)	22.52 (6.796)
	Median	3.00	53.05
	Q1, Q3	1.0, 19.8	10.8, 100.0
	Min, max	0.0, 100.0	0.1, 100.0
	Geometric LS mean ratio (exit/screening) (95% CI)	0.57 (0.46, 0.71)	1.70 (1.28, 2.26)
	Geometric LS mean ratio (AR101/placebo) (95% CI)	0.34 (0.24, 0.48)	
	P-value	< 0.0001	
ps-IgG4 (mgA/L)	Screening DBPCFC		
	n	85	45
	Mean (SD)	1054.118 (2293.6332)	1035.778 (1879.4202)
	Geometric mean (SD)	385.773 (3.8797)	375.874 (3.9267)
	Median	370.0	360.0
	Q1, Q3	120.0, 910.0	100.0, 790.0
	Min, max	70.0, 16900.0	70.0, 8880.0
	Exit DBPCFC		
	n	76	39
	Mean (SD)	8521.316 (12663.5358)	1243.077 (1688.3987)
	Geometric mean (SD)	3396.998 (4.5179)	518.675 (4.6027)
	Median	3570.0	700.0
	Q1, Q3	1205.0, 11200.0	200.0, 1160.0
	Min, max	120.0, 87500.0	10.0, 6250.0
	Geometric LS mean ratio (exit/screening) (95% CI)	10.31 (7.90, 13.45)	1.38 (0.98, 1.95)
	Geometric LS mean ratio (AR101/placebo) (95% CI)	7.47 (4.82, 11.56)	
	P-value	< 0.0001	
ps-IgE/IgG4	Screening DBPCFC		
	n	85	45
	Mean (SD)	0.05 (0.071)	0.12 (0.249)
	Geometric mean (SD)	0.02 (5.540)	0.03 (6.244)
	Median	0.02	0.04

Parameter	Time Point	AR101 (N = 98)	Placebo (N = 48)
	Q1, Q3	0.0, 0.0	0.0, 0.1
	Min, max	0.0, 0.3	0.0, 1.4
	Exit DBPCFC		
	n	76	38
	Mean (SD)	0.00 (0.014)	0.27 (1.139)
	Geometric mean (SD)	0.00 (5.407)	0.04 (6.226)
	Median	0.00	0.05
	Q1, Q3	0.0, 0.0	0.0, 0.1
	Min, max	0.0, 0.1	0.0, 7.1
	Geometric LS mean ratio (exit/screening) (95% CI)	0.05 (0.04, 0.07)	1.38 (0.91, 2.10)
	Geometric LS mean ratio (AR101/placebo) (95% CI)	0.04 (0.02, 0.06)	
	P-value	< 0.0001	

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

Treatment group comparisons of change from screening to exit ($\log_{10}$ scale) were based on an ANCOVA model with terms for treatment group, country, and screening value ($\log_{10}$ scale). Geometric LS mean ratios were converted to the original scale by calculating the antilog of the $\log_{10}$ mean difference.

ANCOVA, analysis of covariance; DBPCFC, double-blind, placebo-controlled food challenge; Ig, immunoglobulin; ITT, intent-to-treat; LS, least squares; Min, max, minimum, maximum; ps, peanut-specific; Q1, Q3, first quartile, third quartile.

- Changes in Peanut Skin Prick Test

The mean wheal diameter in the SPT decreased overall from screening to study exit for the AR101 group compared with the placebo group (Table 9).

Table 9: Change From Baseline in Skin Prick Test in Toddler Study ARC005 (ITT Population, 1 to 3 Years)

Mean Wheal Diameter (mm) [1] Time Point	AR101 (N = 98)	Placebo (N = 48)
Screening		
n	95	48
Mean (SD)	10.76 (5.409)	10.49 (5.440)
Median	9.00	9.75
Q1, Q3	7.00, 13.50	6.75, 13.00
Min, max	4.0, 36.0	2.0, 26.5
Early discontinuation visit		
n	9	3
Mean (SD)	7.94 (3.539)	7.50 (4.272)
Median	8.50	8.00
Q1, Q3	6.50, 11.00	3.00, 11.50
Min, max	0.0, 11.5	3.0, 11.5
Exit visit		
n	80	45
Mean (SD)	6.06 (3.461)	11.97 (7.355)
Median	5.75	11.00
Q1, Q3	4.00, 7.90	7.00, 16.00
Min, max	0.0, 19.5	0.0, 37.5
Change from baseline to exit		

Mean Wheal Diameter (mm) [1] Time Point	AR101 (N = 98)	Placebo (N = 48)
n	77	45
Mean (SD)	-5.05 (5.274)	1.25 (7.079)
Median	-4.00	0.00
Q1, Q3	-7.50, -2.00	-2.50, 5.00
Min, max	-25.0, 4.5	-11.0, 24.0
LS mean change (95% CI) [2]	-5.07 (-6.15, -3.98)	0.86 (-0.57, 2.29)
LS mean difference (AR101 - Placebo) (95% CI) [2]	-5.92 (-7.71, -4.14)	
P-value	< 0.0001	

[1] Mean wheal diameter was 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.

[2] Treatment group comparisons of change from baseline to exit were based on an ANCOVA model with terms for treatment group, country, and baseline value.

ANCOVA, analysis of covariance; ITT, intent-to-treat; LS, least squares; Min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

- Change from Baseline in Single Highest Tolerated Dose of Peanut Protein at DBPCFCs

At the screening DBPCFC, about 85% of subjects in AR101 treatment group and 80% in placebo treatment group tolerated a single highest dose of either 10, 30, or 100 mg peanut protein. At the exit DBPCFC, a substantially higher proportion of the AR101 group tolerated a single highest dose of either 300, 600, 1000, or 2000 mg protein (79.5% AR101, 23% placebo).

In the ITT population, 16 (16.3%) subjects in the AR101 group compared with 24 (50.0%) of subjects in the placebo group had no increase or decrease in the single highest tolerated dose from screening to exit DBPCFC. A total of 82 subjects (83.7%) in the AR101 group compared with 24 subjects (50.0%) in the placebo group had an increase in the single highest tolerated dose from screening to exit DBPCFC (Table 10).

In the completer population, 1 subject (1.2%) in the AR101 group and 21 (46.7%) in the placebo group had no increase or decrease in the single highest dose from screening to exit DBPCFC (Table 11).

A total of 82 subjects (98.8%) in the AR101 group compared with 24 subjects (53.3%) in the placebo group had an increase in the single highest tolerated dose from screening to exit DBPCFC.

Table 10: Change from baseline in the single highest tolerated dose at the exit DBPCFC (ITT population)

	AR101 (N = 98)	Placebo (N = 48)
Single highest tolerated dose at screening DBPCFC		
No dose tolerated	0	0
1 mg [1]	1 (1.0%)	1 (2.1%)
3 mg	13 (13.3%)	8 (16.7%)
10 mg	17 (17.3%)	10 (20.8%)
30 mg	32 (32.7%)	17 (35.4%)
100 mg	35 (35.7%)	12 (25.0%)
300 mg	0	0
Single highest tolerated dose at exit DBPCFC		
No dose tolerated	0	0
1 mg	0	2 (4.2%)
3 mg	2 (2.0%)	7 (14.6%)
10 mg	6 (6.1%)	5 (10.4%)
30 mg	6 (6.1%)	12 (25.0%)
100 mg	6 (6.1%)	11 (22.9%)
300 mg	6 (6.1%)	8 (16.7%)
600 mg	5 (5.1%)	1 (2.1%)
1000 mg	7 (7.1%)	1 (2.1%)
2000 mg	60 (61.2%)	1 (2.1%)
Change in single highest tolerated dose from screening to exit in log_{10} scale [2]		
Mean (SD)	1.38 (0.821)	0.29 (0.970)
Median	1.30	0.24
Q1, Q3	1.00, 1.82	0, 0.76
Min, max	0, 3.30	-2.00, 2.48
Geometric LS mean ratio (exit/screening) (95% CI) [3]	25.41 [17.67, 36.53]	1.69 [1.01, 2.85]
Geometric LS mean ratio (AR101/Placebo) (95% CI) (p-value) [3]	15.01 (7.98, 28.25); p < 0.0001	

Single highest tolerated dose was defined as the highest challenge dose without dose-limiting symptoms and without concomitant medications given. Subjects without an exit DBPCFC were assigned the single highest tolerated dose during the screening DBPCFC.

[1] Subjects had no dose-limiting symptoms at the 3 mg dose and met the protocol inclusion criteria based on dose-limiting symptoms; concurrent medications were given at later doses in the screening DBPCFC.

[2] Subjects who did not tolerate any dose were assigned a single highest tolerated dose of 0.3 mg to calculate log_{10} values.

[3] Treatment group comparisons of change from baseline single highest tolerated dose at the exit DBPCFC (log_{10} mg) were based on an ANCOVA model with terms for treatment group, country, and screening single highest tolerated dose (log_{10} mg). Geometric LS mean ratios were converted to the original scale by calculating the antilog of the log_{10} mean differences.

ANCOVA, analysis of covariance; DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat; LS, least squares; Min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

Table 11: Desensitisation response rate (completer population)

	AR101 (N=83)	Placebo (N=45)
Highest dose tolerated with no more than mild symptoms at exit DBPCFC		
1 mg	0	2 (4.4%)
3 mg	0	5 (11.1%)
10 mg	1 (1.2%)	4 (8.9%)
30 mg	2 (2.4%)	12 (26.7%)
100 mg	2 (2.4%)	11 (24.4%)
300 mg	6 (7.2%)	8 (17.8%)
600 mg	5 (6.0%)	1 (2.2%)
1000 mg	7 (8.4%)	1 (2.2%)
2000 mg	60 (72.3%)	1 (2.2%)
Tolerated a single highest dose of at least 300 mg		
Response rate [95% CI] [1]	78 (94.0%) [86.5%, 98.0%]	11 (24.4%) [12.9%, 39.5%]
Treatment difference (AR101-placebo) [95% CI] (p-value) [2]	69.5% [52.8%, 86.2%] (<0.0001)	
Tolerated a single highest dose of at least 600 mg		
Response rate [95% CI] [1]	72 (86.7%) [77.5%, 93.2%]	3 (6.7%) [1.4%, 18.3%]
Treatment difference (AR101-placebo) [95% CI] (p-value) [2]	80.1% [62.2%, 98.0%] (<0.0001)	
Tolerated a single highest dose of at least 1000 mg		
Response rate [95% CI] [1]	67 (80.7%) [70.6%, 88.6%]	2 (4.4%) [0.5%, 15.1%]
Treatment difference (AR101-placebo) [95% CI] (p-value) [2]	76.3% [58.2%, 94.4%] (<0.0001)	
p-value controlling for geographic region [3]	<0.0001	

- Measurements of Treatment Compliance

Study subjects used diaries to document daily dosing at home and any reactions to the administration of study product. Study product compliance was monitored at study visits by comparing the returned unused study product with the diary records of daily dosing.

Treatment compliance with dosing of study product at home was assessed during up-dosing and maintenance and was high in both treatment groups. The mean number of days where a full or partial dose was consumed at home based on valid diary entries was similar for both treatment groups during up-dosing (97.14 % AR101, 97.11% placebo) and maintenance (96.25% each). The mean percentage of planned dosing days where a dose was missed was less than 4% for both treatment groups during both periods (up-dosing and maintenance).

Ancillary analyses

Supportive Analyses to the Primary Efficacy Endpoint for Toddler (aged 1 to 3 years) Study ARC005

Supportive analyses of desensitisation response rates were conducted based on geographic region for North America and Europe, and the results were consistent with those for the primary efficacy endpoint.

Table 12: Summary of Supportive Analyses to the Primary Efficacy Endpoint by Geographic Region for Study ARC005 (ITT Population, 1 to 3 Years)

	North America		Europe	
Response Rate	AR101 (N = 56)	Placebo (N = 28)	AR101 (N = 42)	Placebo (N = 20)
Proportion of subjects who tolerated 1000 mg peanut protein at the exit DBPCFC (95% CI) [1]	69.6% (55.9, 81.2)	3.6% (0.1, 18.3)	66.7% (50.5, 80.4)	5.0% (0.1, 24.9)
Treatment difference (AR101-placebo) (95% CI) [2]	66.1% (43.4, 88.7)		61.7% (35.1, 88.2)	
P-value [2]	< 0.0001		< 0.0001	

Subjects without an exit DBPCFC were counted as nonresponders.

Treatment difference is AR101 placebo.

[1] Based on exact Clopper-Pearson intervals.

[2] Based on the Farrington-Manning confidence limits.

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

The supportive analysis of desensitisation response rates for the European study population was consistent with the overall ITT results. Of 42 subjects in the ITT population who received AR101, the response rate for the supportive analysis to the primary efficacy endpoint was 66.7% (95% CI: 50.5, 80.4) compared with 5.0% (95% CI: 0.1, 24.9) for 20 subjects who received placebo. Similar statistically significant results were demonstrated in the supportive analysis to the primary efficacy endpoint for the ITT population in the North American region. All supportive analyses in the completer and PP populations were consistent with the supportive results in the ITT population.

Sensitivity Analyses to the Primary Efficacy Endpoint for Europe Estimand

Sensitivity analyses of the primary endpoint for Europe estimand analysed the impact of missing data on the robustness of the results using a worst-case approach to missing data imputation. Sensitivity analyses were also performed to assess the impact of restrictions due to the COVID-19 pandemic: a subgroup analysis that only includes subjects who were on study treatment for up to 64 weeks (maximal allowable duration of up to 40 weeks of up-dosing and 24 weeks of maintenance per the protocol prior to the onset of the pandemic), and a subgroup analysis that excludes subjects who had > 24 weeks of maintenance (maximal allowable duration of maintenance therapy prior to the exit DBPCFC per the protocol prior to the onset of the pandemic). All of the sensitivity analyses were consistent with the overall ITT results.

Table 13: Summary of Sensitivity Analyses to the Primary Efficacy Endpoint for Study ARC005 (1 to 3 Years)

	AR101	Placebo
Worst-case imputation [1]	N = 98	N = 48
Response rate (95% CI), ITT Population [2]	68.4% (58.2, 77.4)	10.4% (3.5, 22.7)
Treatment difference (95% CI) [3]	58.0% (40.7, 75.2)	
P-value [3]	< 0.0001	
Inclusion of subjects with treatment up to 64 weeks due to COVID-19 restrictions	N = 17	N = 15
Response rate (95% CI), ITT Population [2]	88.2% (63.6, 98.5)	6.7% (0.2, 31.9)
Treatment difference (95% CI) [3]	81.6% (46.9, 100.0)	
P-value [3]	< 0.0001	
Exclusion of subjects with more than 24 weeks of maintenance treatment due to COVID-19 restrictions	N = 39	N = 14
Response rate (95% CI), ITT Population [2]	43.6% (27.8, 60.4)	0% (0.0, 23.2)
Treatment difference (95% CI) [3]	43.6% (15.1, 72.1)	
P-value [3]	0.0027	
P-value controlling for geographic region [3]	0.0037	

Treatment difference is AR101-placebo.
[1] AR101-treated subjects without an exit DBPCFC were counted as nonresponders and placebo-treated subjects without an exit DBPCFC were counted as responders.
[2] Based on exact Clopper-Pearson intervals.
[3] Based on the Farrington-Manning confidence limits.
CI, confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat.

In ARC005, the overall median exposure was 12.24 months (range, 0-19 months) for the AR101 group and 12.71 months (range, 4.2-17.3 months) for the placebo group. The median exposure was 2.0 days during initial dose escalation in each treatment groups of AR101 and placebo.

The maximum dose of 300 mg/day was reached by 88 AR101-treated subjects (89.8%) and 45 placebo-treated subjects (93.8%) during up-dosing and was continued by 86 AR101-treated subjects (98.9%) and 45 placebo-treated subjects (100%) during maintenance.

The extent of exposure was longer in some subjects due to the COVID-19 pandemic, as the duration of up-dosing and maintenance treatment for individual subjects were extended to accommodate any delays due to the restrictions on on-site study visits. The product dose level was to be continued or reduced, and dose escalation and food challenges could only be attempted under medical supervision at the study site.

In the safety population (ARC003 Report Body) the median overall exposure was 330.5 days (range, 1-485 days) for the AR101 group and 328.0 days (range, 1-414 days) for the placebo group. The median exposure during the initial dose escalation period was 2 days for both treatment groups. The median exposure during the up-dosing period was 154.0 days (range, 6-278 days) for AR101 and 149.0 days (range, 14-233 days) for placebo. The median exposure during the maintenance period was similar between treatment groups: 175.0 days (range, 15-292 days) for AR101 and 175.5 days (range, 58-250 days) for placebo. A total of 372 AR101-treated subjects had a total of 307.03 years of cumulative exposure to study product, compared with 108.79 years for 124 placebo-treated subjects.

Summary of main study

The following table summarises the efficacy results from the main study 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 14: Summary of efficacy (study ARC005)

Title: Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (POSEIDON)		
Study identifier	ARC005, EudraCT 2018-001749-15, NCT03736447, IND 15463	
Design	Phase 3 study ARC005 was a randomised, double-blind, placebo-controlled study of the efficacy and safety of AR101 in peanut-allergic subjects aged 1 to 3 years conducted in Europe and North America. The primary objective of the study was to assess the efficacy of AR101 in peanut-allergic subjects aged 1 to 3 years. ARC005 was designed to enroll approximately 132 subjects aged 1 to 3 years with a history of sensitivity to peanut. Subjects were to have a sensitivity to peanut, defined as: no known history of peanut ingestion and serum immunoglobulin (Ig) E to peanut of ≥ 5 kUA/L within the 12 months before randomization; or a documented history of peanut allergy and a mean wheal diameter on skin prick test to peanut of at least 3 mm greater than the negative control (diluent) or serum IgE to peanut of ≥ 0.35 kUA/L within the 12 months before randomization. Subjects were to have age-appropriate, dose-limiting allergy symptoms after consuming single doses of peanut protein of > 3 mg to ≤ 300 mg in a screening double-blind, placebo-controlled food challenge (DBPCFC). Subjects with a history of severe or life-threatening anaphylaxis or anaphylactic shock were not eligible for the study. Subjects were also not eligible if they had moderate or severe asthma or mild asthma that was uncontrolled/difficult to control. Eligible subjects were randomly assigned 2:1 to blinded treatment with AR101 or placebo. Randomisation was stratified by geographic region (North America, Europe). The dosing regimen used in this study was almost the same as for study ARC003, differing only in that tolerability was assessed by initial dose escalation of 0.5, 1, 1.5, and 3 mg on Day 1 with an additional single 1 mg dose on Day 2. Subjects who tolerated the 3 mg dose on Day 1 and the 1 mg dose on Day 2 with no more than non-dose-limiting, mild allergy symptoms could enter the up-dosing period. Daily doses of study product administered during up-dosing were 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day; up-dosing could continue for up to 40 weeks. Subjects who tolerated the 300 mg/day dose for 2 weeks within the 40-week up-dosing period began the maintenance period. As for study ARC003, maintenance treatment at 300 mg/day was continued daily for approximately 6 months. After a total of approximately 1 year of blinded treatment (during up-dosing and maintenance treatment), subjects completed an exit DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative) to assess their level of desensitization to peanut allergens.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	Approximately 12 months for each subject Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	AR101	98 subjects
	Placebo	48 subjects

<table>
<tr><td rowspan="5">Endpoints and definitions</td><td>Primary endpoint for Europe estimand</td><td>1000 mg</td><td>Proportion of subjects who tolerated a single dose of at least 1000 mg peanut protein with no more than mild allergy symptoms at the exit DBPCFC</td></tr>
<tr><td rowspan="2">Key secondary endpoints for Europe estimand</td><td>600 mg</td><td>Proportion of subjects who tolerated a single dose of at least 600 mg peanut protein with no more than mild allergy symptoms at the exit DBPCFC</td></tr>
<tr><td>300 mg</td><td>Proportion of subjects who tolerated a single dose of at least 300 mg peanut protein with no more than mild allergy symptoms at the exit DBPCFC</td></tr>
<tr><td rowspan="2">Key exploratory efficacy endpoints</td><td>2000 mg</td><td>Proportion of subjects who tolerated a single highest dose of 2000 mg peanut protein (4043 cumulative) at the exit DBPCFC</td></tr>
<tr><td>Peanut-specific IgE, IgG4, and IgE/IgG4</td><td>Immunologic biomarker changes</td></tr>
<tr><td>Database lock</td><td colspan="3">22 Jul 2022</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">The intent-to-treat (ITT) population for subjects (98 AR101-treated subjects, 100% and 48 placebo-treated subjects, 100%) was used as the primary analysis population for all primary and secondary efficacy endpoints. All subjects received the correct study treatment at randomization. The ITT and safety populations are the same.
All analyses time points are at the exit DBPCFC.</td></tr>
<tr><td></td><td colspan="3"><u>Desensitization response rates</u>
<table>
<tr><th>Europe Estimands</th><th>AR101
(N = 98)</th><th>Placebo
(N = 48)</th></tr>
<tr><td>Primary Efficacy Endpoint</td><td></td><td></td></tr>
<tr><td>Response rate: proportion of subjects who tolerated 1000 mg peanut protein (95% CI) [1]</td><td>68.4%
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<tr><td>P-value [2]</td><td colspan="2">< 0.0001</td></tr>
<tr><td>Key Secondary Efficacy Endpoints</td><td></td><td></td></tr>
<tr><td>Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI) [1]</td><td>73.5%
(63.6, 81.9)</td><td>6.3%
(1.3, 17.2)</td></tr>
<tr><td>Treatment difference (AR101-placebo) [95% CI] [2]</td><td colspan="2">67.2% (50.0, 84.5)</td></tr>
<tr><td>P-value [2]</td><td colspan="2">< 0.0001</td></tr>
<tr><td>Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI) [1]</td><td>79.6%
(70.3, 87.1)</td><td>22.9%
(12.0, 37.3)</td></tr>
<tr><td>Treatment difference (AR101-placebo) [95% CI] [2]</td><td colspan="2">56.7% (39.8, 73.5)</td></tr>
<tr><td>P-value [2]</td><td colspan="2">< 0.0001</td></tr>
<tr><td>Key Exploratory Efficacy Endpoint</td><td colspan="2"></td></tr>
<tr><td>Response rate: proportion of subjects who tolerated 2000 mg peanut protein (95% CI) [1]</td><td>61.2%
(50.8, 70.9)</td><td>2.1%
(0.1, 11.1)</td></tr>
<tr><td>Treatment difference (AR101-placebo) [95% CI] [2]</td><td colspan="2">59.1% (42.1, 76.2)</td></tr>
<tr><td>P-value [2]</td><td colspan="2">< 0.0001</td></tr>
</table></td></tr>
</table>

[1] Based on exact Clopper-Pearson intervals.
[2] Based on the Farrington-Manning confidence limits.

Changes in peanut-specific serum immunoglobulins

Time Point	AR101 (N = 98)	Placebo (N = 48)
ps-IgE (kUA/L)		
Screening		
n	87	45
Geometric mean (SD)	7.04 (6.712)	12.26 (8.429)
Q1, Q3	2.3, 33.5	2.1, 69.7
Exit		
n	76	38
Geometric mean (SD)	3.33 (7.813)	22.52 (6.796)
Q1, Q3	1.0, 19.8	10.8, 100.0
Geometric LS mean ratio (exit/screening) (95% CI)	0.57 (0.46, 0.71)	1.70 (1.28, 2.26)
Geometric LS mean ratio (AR101/placebo) (95% CI)	0.34 (0.24, 0.48)	
P-value	< 0.0001	
ps-IgG4 (mgA/L)		
Screening		
n	85	45
Geometric mean (SD)	385.773 (3.8797)	375.874 (3.9267)
Q1, Q3	120.0, 910.0	100.0, 790.0
Exit		
n	76	39
Geometric mean (SD)	3396.998 (4.5179)	518.675 (4.6027)
Q1, Q3	1205.0, 11200.0	200.0, 1160.0
Geometric LS mean ratio (exit/screening) (95% CI)	10.31 (7.90, 13.45)	1.38 (0.98, 1.95)
Geometric LS mean ratio (AR101/placebo) (95% CI)	7.47 (4.82, 11.56)	
P-value	< 0.0001	
ps-IgE/IgG4		
Screening		
n	85	45
Geometric mean (SD)	0.02 (5.540)	0.03 (6.244)
Q1, Q3	0.0, 0.0	0.0, 0.1
Exit		
n	76	38
Geometric mean (SD)	0.00 (5.407)	0.04 (6.226)
Q1, Q3	0.0, 0.0	0.0, 0.1
Geometric LS mean ratio (exit/screening) (95% CI)	0.05 (0.04, 0.07)	1.38 (0.91, 2.10)
Geometric LS mean ratio (AR101/placebo) (95% CI)	0.04 (0.02, 0.06)	
P-value	< 0.0001	

	Geometric means were calculated by computing the mean on the log_{10} scale and converting the mean to the original scale by calculating the antilog. Treatment group comparisons of change from screening to exit (log_{10} scale) were based on an analysis of covariance (ANCOVA) model with terms for treatment group, country, and screening value (log_{10} scale). Geometric least squares (LS) mean ratios were converted to the original scale by calculating the antilog of the log_{10} mean difference.

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

A pooled analysis or meta-analysis has not been presented by the applicant in this application.

Main data from the main pivotal studies ARC003, ARC010 supporting the efficacy and safety of AR101 as OIT for children aged 4 to 17 years are summarised herein to support AR101 as a desensitisation treatment for peanut-allergic patients aged 1 to 17 years.

Presented efficacy results of both phase 3 study ARC003, and ARC010, demonstrate a statistically significant treatment effect compared with placebo in peanut-allergic subjects aged 4 to 17 years. This treatment effect was observed for the primary and key secondary endpoints of desensitisation response and maximum severity of symptoms for subjects aged 4 to 17 years. Outcomes were further confirmed by supportive and sensitivity subgroup analyses in study ARC003 by paediatric age groups (4-11 years, 12-17 years), geographic region (Europe, North America), and paediatric age groups within each geographic region (except the 12-17-year age group in Europe that had a small number of subjects), as well as in study ARC010 by subgroup analyses by age group (4-11 years, 12-17 years) and country. Supportive secondary endpoint analyses for both studies also demonstrated the benefit of AR101 treatment over placebo in single highest tolerated dose of peanut protein in DBPCFCs, change from baseline in the single highest tolerated dose of peanut protein, use of epinephrine as rescue medication during the DBPCFCs, and changes in peanut-specific antibodies and skin prick test (mean wheal diameter) from baseline to study exit.

The applicant indicated a “better” treatment effect in the younger age group compared to the older children based on the desensitisation response rate at a single dose of 1000 mg peanut protein, the primary endpoint:

ARC005, 1- 3 yrs: 68.4% AR101 and 4.2% placebo; treatment difference, 64.2%

ARC003, 4-17 yrs.: 50.3% AR101 and 2.4% placebo; treatment difference, 47.8%

ARC010, 4-17 yrs.: 58.3% AR101 and 2.3% placebo; treatment difference, 56.0%

Still, when comparing the study design of the three mentioned studies, especially the duration of the maintenance treatment differs, with the shortest maintenance duration in ARC003, followed by ARC010 and is the longest in ARC005.

Clinical studies in special populations

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.

Supportive studies

Supporting data from the phase 2 studies ARC001 and ARC002 had been described and discussed already in the initial MAA procedure of AR101 as OIT for children aged 4 to 17 years, please see EMEA/H/C/004917.

Persistence of efficacy and/or tolerance effects

Data from longer duration of exposure in the primary analysis population of subjects aged 4 to 17 years in study ARC003 is summarised.

Table 15: Duration of exposure in study ARC003 (ITT Population, 4-17 years)

Duration of Exposure (days)	Initial Escalation		Up-Dosing		Maintenance		Overall	
	AR101	Placebo	AR101	Placebo	AR101	Placebo	AR101	Placebo
n	372	124	366	123	310	118	372	124
Median	2.0	2.0	154.0	149.0	175.0	175.5	330.5	328.0
Min, max	1, 2	1, 2	6, 278	14, 233	15, 292	58, 250	1, 485	1, 414

ITT, intent-to-treat; Min, max, minimum, maximum.

Efficacy was assessed in a DBPCFC before study exit, and eligible subjects could enroll in the open-label follow-on study ARC004 to continue (or start) AR101 treatment to explore continued maintenance dosing regimens during extended maintenance.

- Persistence of Efficacy in ARC004 Group 2, Cohort 1

A total of 110 AR101-treated subjects aged 4 to 17 years from ARC003 were enrolled in group 2, cohort 1 of study ARC004 to continue maintenance treatment with AR101 300 mg/day daily for an additional approximately 28 weeks and 103 subjects completed the study. The median overall exposure to AR101 (including exposure in ARC003) was approximately 19 months (580.5 days; range, 388-761 days).

- Desensitisation Response at the ARC004 Exit DBPCFC

Efficacy was assessed for 104 subjects aged 4 to 17 years in group 2, cohort 1 who completed an exit DBPCFC in ARC004. A total of 102 subjects (98.1%) tolerated a single challenge dose of at least 300 mg peanut protein (443 mg cumulative) with no more than mild symptoms, 93 (89.4%) tolerated at least 600 mg peanut protein (1043 mg cumulative), 83 (79.8%) tolerated at least 1000 mg peanut protein (2043 mg cumulative), and 51 (49.0%) tolerated 2000 mg peanut protein (4043 mg cumulative) at the ARC004 exit DBPCFC. Of 37 subjects who tolerated < 1000 mg peanut protein (2043 mg cumulative) at the ARC003 exit DBPCFC, 25 (67.6%) tolerated a higher challenge dose (1000 mg and 2000 mg) at the ARC004 exit DBPCFC. These data demonstrate that clinically meaningful desensitisation is maintained or improved with continued daily maintenance dosing with AR101 300 mg/day.

- Peanut-Specific IgE, IgG4, and IgE/IgG4 Ratio

Of 110 AR101-treated subjects aged 4 to 17 years from ARC003 who continued AR101 maintenance treatment in ARC004 group 2, cohort 1, 104 subjects had peanut-specific IgE measured at screening in ARC003, 103 at the end of up-dosing in ARC003, 96 at study exit in ARC003, and 87 at study exit in ARC004 (Table 16). The geometric mean (SD) peanut-specific IgE was 46.20 (6.439) kUA/L at screening in ARC003, increased to 97.62 (7.781) kUA/L at the end of up-dosing in ARC003, returned to near

baseline value (47.02 [7.308] kUA/L) at study exit in ARC003, and further decreased to 32.93 (5.786) kUA/L at study exit in ARC004.

Table 16: ARC004 Group 2, Cohort 1 Changes in Immunoglobulin Values (4-17 Years)

	ARC003 Screening [1]	ARC003 End of Up-Dosing	ARC003 Exit	ARC004 Exit
Peanut-specific IgE (kUA/L)				
n	104	103	96	87
Mean (SD)	134.31 (189.452)	316.45 (401.549)	163.11 (231.935)	97.86 (157.783)
Geometric mean (SD)	46.20 (6.439)	97.62 (7.781)	47.02 (7.308)	32.93 (5.786)
Median	62.65	159.50	59.30	40.50
Q1, Q3	19.6, 179.5	41.0, 475.0	19.8, 245.5	15.8, 90.0
Min, max	0.1, 1218.0	0.4, 2410.0	0.4, 1230.0	0.1, 967.0
Peanut-specific IgG4 (mgA/L)				
n	96	103	97	80
Mean (SD)	1.018 (2.1322)	6.052 (6.8686)	14.447 (26.8124)	12.422 (10.6885)
Geometric mean (SD)	0.449 (3.5803)	2.726 (4.6706)	4.883 (5.0312)	6.637 (4.1635)
Median	0.530	3.790	5.580	8.590
Q1, Q3	0.17, 1.09	1.29, 8.22	2.41, 13.10	3.29, 20.35
Min, max	0.03, 19.50	0.07, 30.00	0.07, 199.00	0.07, 30.00
Peanut-specific IgE/IgG4 ratio				
n	96	103	96	80
Mean (SD)	362.54 (809.186)	101.24 (217.200)	32.66 (61.459)	31.23 (128.459)
Geometric mean (SD)	106.45 (5.890)	35.81 (4.535)	9.58 (5.451)	4.80 (6.203)
Median	139.83	39.78	12.46	5.10
Q1, Q3	36.0, 358.6	12.5, 105.5	2.3, 29.9	1.2, 16.0
Min, max	1.0, 6592.9	1.0, 1914.3	0.2, 339.0	0.1, 1105.7

[1] ARC003 inclusion criteria required meeting a threshold for total IgE and/or skin prick test; thus, minimum values in the range of values could be below the threshold requirement for each test.

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

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

AR101 is authorised as OIT for children aged 4 to 17 years. This submission presents data from younger patients (study ARC005) to support extending the indication from children aged 4 to 17 to children and toddlers aged 1 to 17 years. Therefore, comparison in-between studies will be made.

The Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (POSEIDON), Protocol Identifier ARC005 is a pivotal randomised, double-blind, placebo-controlled multicentre phase 3 study of the efficacy and safety of AR101 in peanut-allergic toddlers aged 1 to 3 years conducted at 14 study sites in North America and 9 in Europe.

Besides few differences in the ARC005 study design, the study was performed with a similar design as in the previous studies ARC003 and ARC010 for children aged 4 years and above. Differences were a slightly lower starting dose for up-dosing (1 mg for 1-3 years while 3 mg was used for 4-17 years), length of the study (slightly longer) to up dose to a 300 mg highest dose before maintenance period, and a higher endpoint challenge dose (of 2000 mg peanut protein single dose, as an exploratory endpoint).

In study ARC005 study in– and exclusion criteria, study objectives and endpoints including assessment of efficacy endpoints by performing DBPCFC were rather the same as for study ARC003 and ARC010. However, certain adaptations had been made in order to reflect the different age population of 1-3 years old children. As such, in ARC003 and ARC010, subjects had to have a serum IgE to peanut of ≥ 0.35 kUA/L and/or a SPT to peanut of ≥ 3 mm compared with negative control at screening, and in ARC003 dose-limiting symptoms at single challenge doses of ≤ 100 mg peanut protein / in ARC010, dose-limiting symptoms at single challenge doses of ≤ 300 mg peanut protein in the screening DBPCFC.

In ARC005, subjects were to have a sensitivity to peanut, defined as: no known history of peanut ingestion and serum IgE to peanut of ≥ 5 kUA/L within the 12 months before randomisation, or a documented history of peanut allergy and a mean wheal diameter on SPT to peanut of at least 3 mm greater than the negative control or serum IgE to peanut of ≥ 0.35 kUA/L within the 12 months before randomisation. Eligible subjects were to have age-appropriate, dose-limiting allergy symptoms after consuming single doses of peanut protein of > 3 mg to ≤ 300 mg in the screening DBPCFC before being randomly assigned 2:1 to AR101 or placebo. In terms of performance of the DBPCFC, subtle specific food challenge stopping criteria were implemented in ARC005 (specified as including ear picking, tongue rubbing, putting a hand in the mouth, and neck scratching), as in subjects aged < 4 years allergy symptoms can be difficult to interpret.

From the statistical point of view, sample size considerations, randomisation procedure, including stratification by region (in line with ICH-E17) are acceptable. Assumptions for drop-out and early discontinuation are considered very high (25%), considering that this is a study with small infants. In terms of the statistical analysis method, it is noted that two different primary endpoints and testing hierarchies were defined for the US and Europe. Although it is understood that regulatory requirements may be different across different regions, inconsistent results would have raised uncertainty. No discussion of reasons for or implication of this design choice was included in the study protocol. Furthermore, there is no explicit prospective discussion of clinical relevance. However, for the US, a margin of 15% for the risk difference was defined which is considered to resemble an approach to clinical relevance.

Ultimately, a total of 289 subjects were screened and 146 were randomly assigned to study treatment (98 to AR101 and 48 to placebo). Of these, 83 of 98 (84.7%) AR101 subjects and 45 of 48 (93.8%) placebo subjects completed the study. This means, that more than twice as much subjects discontinued treatment in the AR101 group (15.3%), compared to 6.2% in placebo. The most common reasons for study discontinuation in the AR101 group were subject withdrew consent (5, 5.1%) and adverse events (5, 5.1%).

In total four global Protocol Amendments had been made. The primary purpose were modifications of eligibility criteria especially based on considerations dealing with the young age of included study participants. Other reasons were based on adding guidance to change the study conduct during the

COVID-19 pandemic. A total of 37 subjects (25.3%) had 1 or more major protocol deviations (29 subjects [29.6%] AR101, 8 subjects [16.7%] placebo). Additional analyses suggest that the protocol deviations did not have a major impact on study objectives, efficacy results or interpretation of study results.

Demographic and baseline characteristics were matched between treatment groups. The median age of the 146 subjects was 2.0 years (IQR, 1-3 years), the same for both groups. However, following imbalances were noted: most subjects were male (58.2% AR101, 58.3% placebo), were white (67.3% AR101, 66.7% placebo) and were not of Hispanic or Latino ethnicity (76.5% AR101, 64.6% placebo). More subjects were enrolled in North America (57.5%) compared with Europe (42.5%). Still, the randomised treatment assignment was similar between geographic region (57.1% AR101 and 58.3% placebo in North America, 42.9% AR101 and 41.7% placebo in Europe).

More importantly, the baseline median peanut-specific IgE and Ara h 2 IgE levels were numerically lower in the AR101 group (6.8 kUA/L and 5.190 kUA/L, respectively) compared with the placebo group (30.0 kUA/L and 14.200 kUA/L). These numerically higher values of sIgE and Ara h2-IgE between the AR101 and the placebo group are striking (media sIgE: of 6.8 kU/L vs 30k/A/L; median Ara h2 5.190 kU/L vs 14.200 kUA/L). According to the literature, high Ara h 2-IgE levels are associated with peanut allergy, and a sensitisation against peanut-components, such as Ara h1 and Ara h3 in parallel, are assumed to correlate with the likelihood of more severe allergic reactions upon peanut contact (Peters et al. 2007; Flinterman et al. 2008; Astier et al. 2006). As the values of total IgE with 162.5 U/ml and 175 U/ml are rather comparable between the groups, the peanut-specific sensitisation profile was further underlined. The median mean wheal diameter in the screening SPT to peanut was: AR101 median 9.0 mm (range, 4-36 mm), placebo median 9.75 mm (range, 2-26.5 mm).

Regarding the baseline DBPCFC one may assume that participants in the placebo group reacted at slightly lower doses: as such the single highest tolerated dose was 13.3% vs 16.8% at 3mg; 17.3% vs 20.8% at 10 mg, 35.7% vs 25% at 100mg. Thus, about 85% of subjects in AR101 treatment group and 80% in placebo treatment group tolerated a single highest dose of either 10, 30, or 100 mg peanut protein. Still, as the median single highest tolerated dose was 30 mg in both groups, the distribution of study participants is regarded as acceptable. Consequently, it was elucidated further if and to which extent observed imbalance in baseline parameters may potentially influence the treatment effect. Therefore, an updated analysis controlling for the multiple baseline variables (ps-IgE, ps-IgE/IgG4 ratio, Ara h 1 IgE, Ara h 2 IgE, Ara h 3 IgE, Ara h 9 IgE, and Ara h 9 IgG4) was performed. It was shown that the baseline imbalance in *in vitro* sensitisation parameters did not substantially affect treatment effect estimates for the primary or relevant secondary study outcomes.

Efficacy data and additional analyses

The efficacy results demonstrate a statistically significant treatment effect of AR101 compared with placebo in subjects aged 1 to < 4 years. This effect was observed for the primary and key secondary endpoints of desensitisation response and maximum severity of symptoms. Outcomes were confirmed by supportive and sensitivity subgroup analyses by subjects for geographic region (North America, Europe) and exploratory efficacy endpoints. The desensitisation response rates exceeded the (US) prespecified margin of 15%. Efficacy endpoints in Completer and PP populations were consistent with results in the ITT population.

Primary endpoint

For the primary endpoint, the desensitisation response rate at a single dose of 1000 mg was 68.4% for AR101 and 4.2% for placebo; treatment difference, 64.2% (95% CI: 47.0, 81.4; p < 0.0001).

Key secondary endpoints

For the key secondary endpoints, 1) the desensitisation response rate at a single dose of 600 mg was 73.5% for AR101 and 6.3% for placebo; treatment difference, 67.2% (95% CI: 50.0, 84.5; p < 0.0001), 2) the desensitisation response date at a single dose of 300 mg was 79.6% AR101 and 22.9% placebo; treatment difference, 56.7% (95% CI: 39.8, 73.5; p < 0.0001).

Treatment with AR101 also resulted in a statistically significant treatment effect over placebo in the proportion of subjects who tolerated a single highest dose of at least 2000 mg peanut protein with no more than mild symptoms at the exit DBPCFC (p < 0.0001), and the maximum severity of symptoms at any challenge dose of peanut protein observed at the exit DBPCFC was reduced for subjects treated with AR101 compared with placebo (p < 0.0001).

It is noted that although 300 mg daily dose of study product had to be tolerated for at least 2 consecutive weeks before having the DBPCFC, still several subjects did not tolerate 3 mg, 10 mg, 30mg, 100 mg or 300 mg at the exit challenge – not only in the ITT population (defined as participants who received at least one treatment) but also in the completer population. As such, in the ITT population n=20 subjects tolerated 10 mg, 30 mg or max. 100 mg as single highest dose of the exit DBPCFC; in the completer population n=5, and in the PP n=4. This means at least for the subjects in the completer and PP population that although these subjects tolerated their maintenance dose, they did not tolerate 300 mg during DBPCFC. In the context of the response to supplementary information, the applicant explained that in his opinion these data represent false positive results as former described in literature. For example, anxiety on the test day with associated flaring of eczema, urticaria, and/or subjective throat tightness could be interpreted as evidence of a positive challenge. In addition, challenge results might had been true positives, reflecting an unexpected change in reaction threshold in terms of e.g. the presence of co-factors on the challenge day (e.g., viral upper respiratory infection, poor sleep). However, since all subjects successfully tolerated 300 mg of Palforzia prior to the challenge, it was regarded as unlikely that this would dramatically reverse with short-term poor adherence. Although, the argumentation is followed, the below described changes might be interpreted with caution:

Change in single Highest Tolerated Dose

In the ITT population,

- 16 (16.3%) (AR101) compared with 24 (50.0%) (Placebo) had no change in the single highest tolerated dose from screening to exit DBPCFC and
- 82 subjects (83.7%) (AR101) compared with 24 subjects (50.0%) (Placebo) had an increase in the single highest tolerated dose from screening to exit DBPCFC.

In the Completer Population, 82 subjects (98.8%) (AR101) compared with 24 subjects (53.3%) (Placebo) had an increase in the single highest tolerated dose from screening to exit DBPCFC.

Thus, no decrease in the placebo group, ITT, has been described, but 50% of the placebo group had an increase in the tolerated dose from screening to exit, from which n = 1 even tolerated up to 2000 mg peanut protein at the exit challenge.

Secondary endpoints - Peanut-Specific Immunoglobulins and SPT

In terms of the level of peanut-specific IgE, there was a trend of decrease from screening to exit in the AR101 group, while in the Placebo group the trend was an increase from screening to exit. The mean wheal diameter in the SPT decreased from screening to study exit for the AR101 group compared with the placebo group.

Early discontinuations

It is noted that 83 of 98 (84.7%) AR101 subjects and 45 of 48 (93.8%) placebo subjects completed the study. This means, that more than twice as much subjects discontinued treatment in the AR101 group (15.3%), compared to 6.2% in placebo.

A summary of subjects who discontinued early showed that the (available) median baseline ps-IgE and Ara h2 IgE of the AR101-treated subjects were higher (71 Ku/L, 66.7 Ku/L) than the median of all AR101-treated subjects (6.8 Ku/L, 5.19 Ku/L). A pronounced discontinuation during up-dosing indicates a clinical connection with the AR101 treatment. During up-dosing, more treatment related adverse events had been described. As such, twice as much subjects (n=10) discontinued during the up-dosing phase compared to the maintenance phase (n=5).

Duration of exposure and treatment Compliance

The median overall exposure was indicated with 12.24 months (range, 0-19 months) for the AR101 group and 12.71 months (range, 4.2-17.3 months) for the placebo group. The duration of exposure is striking, considering that with up to 19-month overall treatment, the duration is about twice as long as for instance in study ARC010 in 4-17 years olds (ARC010 in total approximately 9 month). In ARC005, the median overall exposure was depicted with 372 days (range, 6-577 days) for the AR101 group and 386.5 days (range, 128-527 days) for the placebo group. Duration of exposure for more than 365 days and up to >532 days was indicated for about 55% of subjects in the AR101 group. This extent of exposure in a number of subjects was explained due to the COVID-19 pandemic, as the duration of up-dosing and maintenance treatment for individual subjects were extended to accommodate any delays due to the restrictions on on-site study visits. In opposite in ARC003 (Report Body), duration of exposure for subjects treated with AR101 was depicted with >364 days for 16.3% only. Additional controlling for age and total study drug exposure does not change statistical significance of the analysis. However, as discussed in more detail above, some differences are noted in the treatment effect estimates in the various models. Whether age or exposure would be the driving factor cannot be satisfactorily evaluated. Nevertheless, since the effect estimates tend towards a higher effect (if affected) the CHMP does not see the need to further investigate.

Concerning treatment compliance with dosing of study product at home, the mean number of days where a full or partial dose was consumed, was similar for both treatment groups. The mean percentage of planned dosing days where a dose was missed was less than 4% for both groups during up-dosing and maintenance.

In summary, efficacy results of both phase 3 study ARC003, and ARC010, demonstrated a statistically significant treatment effect compared with placebo in peanut-allergic subjects aged 4 to 17 years. The results of the toddler trial ARC005, are numerically better compared with results gained in ARC003 and ARC010, with desensitisation response rates at a single dose of 1000 mg peanut protein (the Primary Endpoint) with in

- ARC005, 1- 3 yrs: 68.4% AR101 and 4.2% placebo; treatment difference, 64.2%
- ARC003, 4-17 yrs.: 50.3% AR101 and 2.4% placebo; treatment difference, 47.8%
- ARC010, 4-17 yrs.: 58.3% AR101 and 2.3% placebo; treatment difference, 56.0%

Still, when comparing the study conduct of these three studies, especially the duration of the maintenance treatment differs. The shortest maintenance duration occurred in ARC010, followed by ARC003 and the longest maintenance duration appeared in ARC005. The latter prolonged treatment phases has been attributed to the pandemic in particular. To explore prolonged maintenance treatment, (previous) data from the open-label follow-on study ARC004 may be used. Here, prolonged treatment had been described of further improving the efficacy: Changes in peanut-specific IgE, IgG4, and IgE/IgG4 ratio from ARC003 study exit to ARC004 study exit demonstrated continued modulation

of immunoglobulin levels. In addition, the reduction in SPT mean wheal diameter from ARC003 screening to ARC003 study exit was sustained.

Interestingly, these further improved treatment effects in the 4 to 17 years olds after prolonged treatment duration (total treatment longer than 12 months), fit well with the “better” results of the 1 to 3-year-old children analysed in study ARC005. For many children in ARC005 the overall treatment duration was clearly longer than 12 months due to the pandemic. Thus, the “better” effect observed in the younger children may rather/also be explained by the longer duration of treatment than the age of the children. Additional analyses suggest that the extent of drug exposure for a number of ARC005 subjects due to the COVID-19 pandemic did not change the statistical significance of the analysis. However, as discussed in more detail above, some differences are noted in the treatment effect estimates in the various models. Whether age or exposure would be the driving factor cannot be satisfactorily evaluated. Nevertheless, since the effect estimates tend towards a higher effect (if affected) the assessors do not see the need to further investigate.

Data on longer treatment duration have been reviewed in a separate post-authorisation measure (P46/011) with Study ARC008, an open-label follow-on study for AR101 studies listed as category 3 study in the RMP. The results did not raise any new safety concerns.

2.4.4. Conclusions on the clinical efficacy

The findings of the phase 3 toddler study ARC005, indicate that AR101 treatment is associated with a statistically significant treatment effect compared with placebo in peanut-allergic subjects aged 1 to 3 years. This treatment effect was observed for the primary and key secondary endpoints of desensitisation response and maximum severity of symptoms.

Additional analyses showed that the baseline imbalance in *in vitro* sensitisation parameters did not substantially affect treatment effect estimates for the primary or relevant secondary study outcomes. The extent of drug exposure for a number of ARC005 subjects due to the COVID-19 pandemic did not change the statistical significance of the analysis, as shown by additional controlling for age and total study drug exposure. However, as discussed in more detail above, some differences are noted in the treatment effect estimates in the various models. Whether age or exposure would be the driving factor cannot be satisfactorily evaluated. Nevertheless, since the effect estimates tend towards a higher effect (if affected) the CHMP do not see the need to further investigate at this time point.

CHMP considered that the clinical efficacy data supports the extension of indication for the treatment of patients aged from 1 to 3 years with a confirmed diagnosis of peanut allergy.

2.5. Clinical safety

Introduction

In the summary of clinical safety (SCS) for patients aged 4 to 17 years, the safety profile of AR101 in patients with peanut allergy was derived from the following 5 clinical studies involving 944 unique subjects aged 4 to 17 years who received at least 1 dose of AR101 study product:

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

Together these 5 studies include 841 subjects treated with AR101 and 335 subjects treated with placebo in the combined controlled population (hereafter, controlled population), and 944 subjects treated with AR101 that make up the population of all treated subjects from these studies (hereafter, integrated safety population). This integrated safety population is considered representative of the peanut-sensitive population that is likely to be treated with the licensed product.

The safety data from ARC005 are not integrated with the other studies presented in this submission and are presented separately within each section. Therefore, the “new” safety data with focus on children aged 1 to 3 years (ARC005) are presented in this section.

Subject disposition

In Study ARC005, in the safety population, 83 of 98 (84.7%) subjects in the AR101 group and 45 of 48 (93.8%) subjects in the placebo group completed the study. The most common reasons for study discontinuation in the AR101 group were subject withdrew consent and adverse event (5 of 98 subjects [5.1%] each). Other reasons for study treatment discontinuation were reported for 4 (4.1%) or fewer subjects in either treatment group. No subject discontinued the study due to a protocol violation or sponsor decision. No subjects discontinued due to the Coronavirus Disease 2019 pandemic. No subject died during the study.

Patient exposure

In Study ARC005, the overall median exposure was 12.24 months (range, 0.2-19.0 months) for the AR101 group and 12.71 months (range, 4.2-17.3 months) for the placebo group. The median exposure was 2.0 days during initial dose escalation in each treatment groups of AR101 and placebo. During up-dosing the median exposure was 177.5 days (range, 4-529 days) for AR101 and 185.5 days (range, 126-336 days) for placebo. The median exposure during maintenance was 188.0 days (range, 9-406 days) for the AR101 group and 187.0 days (range, 109-346 days) for the placebo group. The cumulative exposure was 98.42 years for the AR101 group and 52.38 years for the placebo group.

The maximum dose of 300 mg/day was reached by 88 AR101-treated subjects (89.8%) and 45 placebo-treated subjects (93.8%) during up-dosing and was continued by 86 AR101-treated subjects (98.9%) and 45 placebo-treated subjects (100%) during maintenance. The median time to the 80 mg daily dose was 99.5 days for the AR101 group and 100.0 days for the placebo group, and the median time to the 300 mg daily dose was 188.0 days for the AR101 group and 189.0 days for the placebo group.

Table 17: Extent of Exposure in Study ARC005 (Safety Population, 1 to 3 Years)

Parameter	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Duration of exposure (months) [1]								
Mean (SD)	0.07 (0.000)	0.07 (0.000)	6.34 (2.310)	6.73 (1.846)	6.37 (2.248)	6.74 (1.906)	12.07 (3.715)	13.11 (2.728)
Median	0.07	0.07	5.84	6.10	6.18	6.15	12.24	12.71
Q1, Q3	0.07, 0.07	0.07, 0.07	5.26, 7.11	5.28, 7.37	5.33, 6.88	5.72, 7.34	11.51, 14.05	11.40, 15.48
Min, max	0.1, 0.1	0.1, 0.1	0.1, 17.4	4.1, 11.1	0.3, 13.4	3.6, 11.4	0.2, 19.0	4.2, 17.3
Duration of exposure (days) [1]								
Mean (SD)	2.0 (0.00)	2.0 (0.00)	192.7 (70.24)	204.5 (56.12)	193.8 (68.35)	204.9 (57.95)	366.8 (112.94)	398.6 (82.92)
Median	2.0	2.0	177.5	185.5	188.0	187.0	372.0	386.5
Q1, Q3	2.0, 2.0	2.0, 2.0	160.0, 216.0	160.5, 224.0	162.0, 209.0	174.0, 223.0	350.0, 427.0	346.5, 470.5
Min, max	2, 2	2, 2	4, 529	126, 336	9, 406	109, 346	6, 577	128, 527
Maximum dose reached (mg/day)								
Mean (SD)	6.0 (0.00)	6.0 (0.00)	273.0 (82.66)	290.4 (42.87)	300.7 (6.43)	300.0 (0.00)	273.7 (82.91)	290.4 (42.87)
Median	6.0	6.0	300.0	300.0	300.0	300.0	300.0	300.0
Q1, Q3	6.0, 6.0	6.0, 6.0	300.0, 300.0	300.0, 300.0	300.0, 300.0	300.0, 300.0	300.0, 300.0	300.0, 300.0
Min, max	6, 6	6, 6	1, 300	40, 300	300, 360	300, 300	6, 360	40, 300
Maximum dose reached by category (mg/day)								
0.5	0	0	0	0	0	0	0	0
1	0	0	1 (1.0%)	0	0	0	0	0
1.5	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
6	98 (100.0%)	48 (100.0%)	6 (6.1%)	0	0	0	7 (7.1%)	0

Parameter	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
12	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0
40	0	0	1 (1.0%)	1 (2.1%)	0	0	1 (1.0%)	1 (2.1%)
80	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
160	0	0	0	1 (2.1%)	0	0	0	1 (2.1%)
200	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
240	0	0	0	1 (2.1%)	0	0	0	1 (2.1%)
300	0	0	88 (89.8%)	45 (93.8%)	86 (98.9%)	45 (100.0%)	87 (88.8%)	45 (93.8%)
360	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Time to 80 mg dosing (days) [2]								
Median (95% CI)							99.5 (93.0, 106.0)	100.0 (91.0, 114.0)
Time to 300 mg dosing (days) [2]								
Median (95% CI)							188.0 176.0, 198.0)	189.0 (171.0, 206.0)

[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.

[2] Calculated using Kaplan-Meier methodology. Subjects not reaching the specified dose were censored at the date of the last study product dose.

CI, confidence interval, CSR, Clinical Study Report; min, max, minimum, maximum; Q1, Q3, first quartile, third quartile.

Demographics in Study ARC005

As presented above and in the clinical efficacy section, the median age of the 146 subjects was 2.0 years (interquartile range, 1-3 years), the same for both groups (AR101 and placebo). 49 subjects (33.6%) were aged 1 to < 2 years (33.7% AR101, 33.3% placebo), 50 subjects (34.2%) were aged 2 to < 3 years (35.7% AR101, 31.3% placebo), and 47 subjects (32.2%) were aged 3 to < 4 years (30.6% AR101, 35.4% placebo). Most subjects were male (58.2% AR101, 58.3% placebo), were white (67.3% AR101, 66.7% placebo) and were not of Hispanic or Latino ethnicity (76.5% AR101, 64.6% placebo).

However, both the baseline median peanut-specific IgE and Ara h 2 IgE were numerically lower in the AR101 group (6.8 kUA/L and 5.190 kUA/L, respectively) compared with the placebo group (30.0 kUA/L and 14.200 kUA/L). The median mean wheal diameter in the SPT test to peanut, was 9.0 mm (range, 4-36 mm) for the AR101 group and 9.75 mm (range, 2-26.5 mm) for the placebo group.

The single highest tolerated dose of peanut protein at the screening DBPCFC was 13.3% vs 16.8% at 3 mg; 17.3% vs 20.8% at 10 mg, 35.7% vs 25% at 100mg, in all 30 mg for 32.7% of the AR101 group and 35.4% of the placebo group. Thus, about 85% of subjects in AR101 treatment group and 80% in placebo treatment group tolerated a single highest dose of either 10, 30, or 100 mg peanut protein. As such, at the baseline DBPCFC participants in the placebo group seem to react at slightly lower doses at screening and their baseline median peanut-specific IgE and Ara h 2 IgE levels were numerically higher compared to subjects in the AR101 group.

The peanut allergy related history, like median time since the most recent allergic reaction to peanut was 9.47 months and was comparable in the AR101 group (8.96 months) than the placebo (10.58 months).

Overall, a similar proportion of subjects in each treatment group had eczema/atopic dermatitis or asthma as reported in both the medical history and allergic history other than peanut case report form.

Adverse events

In the safety population (98 AR101, 48 placebo), 98.0% of AR101 and 97.9% of placebo subjects had 1 or more adverse events:

- During initial dose escalation, 21.4% AR101, 20.8% placebo
- During up-dosing, 98.0% AR101, 97.9% placebo
- During maintenance, 90.8% AR101, 91.1% placebo

The overall exposure-adjusted adverse event rate (total number of events divided by the total number of subject-years at risk) was 24.18 events per subject-year for AR101 and 18.33 for placebo.

Most adverse events were of mild or moderate intensity (severity) (92.8% in AR101 group and 93.7% in placebo).

Overall, 80 AR101-treated subjects (81.6%) and 36 placebo-treated subjects (75.0%) had events considered allergic in nature (hypersensitivity events):

- During initial dose escalation, 15.3% AR101, 6.3% placebo
- During up-dosing, 70.4% AR101, 66.7% placebo
- During maintenance, 51.7% AR101, 51.1% placebo

Adverse events associated with a food allergen exposure were reported in 41 subjects in the AR101 group (41.8%) compared with 22 subjects in the placebo group (45.8%).

Table 18: Overall Summary of Treatment-Emergent Adverse Events in Study ARC005 (Safety Population, 1 to 3 Years)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Total exposure (years)	0.55	0.26	51.71	26.87	46.16	25.25	98.42	52.38
Total adverse events	49	16	1637	682	694	262	2380	960
Total serious adverse events	0	0	3	0	4	2	7	2
Subjects with at least 1 adverse event	21 (21.4%)	10 (20.8%)	96 (98.0%)	47 (97.9%)	79 (90.8%)	41 (91.1%)	96 (98.0%)	47 (97.9%)
By maximum severity [1]								
Grade 1: Mild	20 (20.4%)	10 (20.8%)	64 (65.3%)	38 (79.2%)	55 (63.2%)	29 (64.4%)	50 (51.0%)	29 (60.4%)
Grade 2: Moderate	1 (1.0%)	0	30 (30.6%)	9 (18.8%)	21 (24.1%)	10 (22.2%)	41 (41.8%)	16 (33.3%)
Grade ≥ 3: Severe or higher	0	0	2 (2.0%)	0	3 (3.4%)	2 (4.4%)	5 (5.1%)	2 (4.2%)
By relationship to study product [2]								
Not related	6 (6.1%)	7 (14.6%)	29 (29.6%)	20 (41.7%)	49 (56.3%)	34 (75.6%)	22 (22.4%)	19 (39.6%)
Related	15 (15.3%)	3 (6.3%)	67 (68.4%)	27 (56.3%)	30 (34.5%)	7 (15.6%)	74 (75.5%)	28 (58.3%)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Adverse events leading to study product discontinuation	0	0	5 (5.1%)	0	2 (2.3%)	0	6 (6.1%)	0
Adverse events requiring dose interruption of study product	0	0	53 (54.1%)	25 (52.1%)	45 (51.7%)	23 (51.1%)	68 (69.4%)	31 (64.6%)
Adverse events requiring dose reduction of study product	0	0	14 (14.3%)	4 (8.3%)	7 (8.0%)	1 (2.2%)	18 (18.4%)	5 (10.4%)
Anaphylactic reaction [3]	0	0	2 (2.0%)	2 (4.2%)	6 (6.9%)	2 (4.4%)	8 (8.2%)	4 (8.3%)
Hypersensitivity event [4]	15 (15.3%)	3 (6.3%)	69 (70.4%)	32 (66.7%)	45 (51.7%)	23 (51.1%)	80 (81.6%)	36 (75.0%)
Adverse event associated with food allergen exposure	2 (2.0%)	1 (2.1%)	32 (32.7%)	15 (31.3%)	22 (25.3%)	13 (28.9%)	41 (41.8%)	22 (45.8%)
Subjects with at least 1 serious adverse event	0	0	3 (3.1%)	0	3 (3.4%)	2 (4.4%)	6 (6.1%)	2 (4.2%)
Serious adverse events by maximum severity [1]								
Grade 1: Mild	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Grade 2: Moderate	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Grade ≥ 3: Severe or higher	0	0	2 (2.0%)	0	2 (2.3%)	2 (4.4%)	4 (4.1%)	2 (4.2%)
Serious adverse events by relationship to study product [2]								
Not related	0	0	3 (3.1%)	0	3 (3.4%)	2 (4.4%)	6 (6.1%)	2 (4.2%)
Related	0	0	0	0	0	0	0	0
Exposure-adjusted event rates, events (rate) [5]								
Total adverse events (event rate)	49 (88.60)	16 (60.88)	1637 (31.66)	682 (25.38)	694 (15.03)	262 (10.38)	2380 (24.18)	960 (18.33)
Related to study product	33 (59.67)	7 (26.63)	576 (11.14)	171 (6.36)	140 (3.03)	13 (0.51)	749 (7.61)	191 (3.65)
Severe or higher	0	0	3 (0.06)	0	4 (0.09)	2 (0.08)	7 (0.07)	2 (0.04)
Anaphylactic reactions [3]	0	0	3 (0.06)	2 (0.07)	6 (0.13)	2 (0.08)	9 (0.09)	4 (0.08)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Adverse events that are hypersensitivity events [4]	35 (63.29)	5 (19.02)	739 (14.29)	233 (8.67)	244 (5.29)	67 (2.65)	1018 (10.34)	305 (5.82)
Adverse events leading to discontinuation of study product	0	0	7 (0.14)	0	3 (0.06)	0	10 (0.10)	0
Adverse events requiring dose interruption of study product	0	0	235 (4.54)	81 (3.01)	130 (2.82)	65 (2.57)	365 (3.71)	146 (2.79)
Adverse events requiring dose reduction of study product	0	0	40 (0.77)	5 (0.19)	11 (0.24)	1 (0.04)	51 (0.52)	6 (0.11)
Serious adverse events	0	0	3 (0.06)	0	4 (0.09)	2 (0.08)	7 (0.07)	2 (0.04)
Serious adverse events related to study product	0	0	0	0	0	0	0	0
Serious adverse events with severity of severe or higher	0	0	2 (0.04)	0	3 (0.06)	2 (0.08)	5 (0.05)	2 (0.04)

[1] Subjects with more than 1 adverse event were counted only once using the maximum severity.

[2] Subjects with more than 1 adverse event were counted only once using the closest relationship to study product.

[3] None of the reported reactions were classified as severe.

[4] Defined as adverse events that were considered by investigators to be allergic reactions.

[5] Defined as the total number of events divided by the total number of subject-years at risk during the period.

CSR, Clinical Study Report.

Common adverse events by Preferred Terms

The most common adverse events (≥ 20% of subjects in either treatment group overall with ≥ 5% higher incidence in the AR101 group) in decreasing order were cough, vomiting, pyrexia, rhinorrhea, upper respiratory tract infection, diarrhea, and abdominal pain, and the incidence of each decreased substantially from up-dosing to maintenance.

- During initial dose escalation, no adverse events reached 20% incidence and no events were ≥ 5% higher in the AR101 group.
- During up-dosing, cough (43.9% AR101, 31.3% placebo), vomiting (41.8% AR101, 22.9% placebo), rhinorrhea (29.6% AR101, 22.9% placebo), diarrhea (31.6% AR101, 22.9% placebo), and abdominal pain (21.4% AR101, 10.4% placebo) were the only overall common events that reached ≥ 20% incidence in the AR101 group with ≥ 5% higher incidence over the placebo group. Pyrexia, upper respiratory tract infection, and erythema reached ≥ 20% incidence in the AR101 group but were not ≥ 5% higher over the placebo group.
- During maintenance, vomiting (28.7% AR101, 15.6% placebo) and upper respiratory tract infection (23.0% AR101, 17.8% placebo) were the only overall common events that reached ≥ 20% incidence in the AR101 group with ≥ 5% higher incidence over the placebo group. Pyrexia reached ≥ 20% incidence in the AR101 group but was not ≥ 5% higher over the placebo group. Other common events with ≥ 5% higher incidence in the AR101 group were rhinitis and ear infection.

When Common Adverse Events Adjusted for Exposure: The most frequent exposure-adjusted adverse event rates overall were urticaria (2.63 events per subject-year AR101, 2.20 placebo), cough (1.96 AR101, 1.03 placebo), and pyrexia (1.15 each AR101 and placebo).

When adjusted for exposure, the most frequent adverse event rate with the highest difference between groups of ≥ 0.5 events per subject-year was sneezing with a difference in event rate between AR101 and placebo of 1.31 events per subject-year (AR101, 1.69 events per subject-year vs placebo, 0.38 events per subject-year). Other adverse events with a difference between groups of ≥ 0.5 events per subject-year were cough (0.93) and vomiting (0.61). The exposure adjusted event rates for all of these adverse events decreased substantially from up-dosing to maintenance.

Table 19: Treatment-Emergent Adverse Events in ≥ 5% of Subjects in Either Treatment Group Overall by Preferred Term in Study ARC005 (Safety Population, 1 to 3 Years)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
Preferred Term	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with at least 1 adverse event	21 (21.4%)	10 (20.8%)	96 (98.0%)	47 (97.9%)	79 (90.8%)	41 (91.1%)	96 (98.0%)	47 (97.9%)
Cough	2 (2.0%)	0	43 (43.9%)	15 (31.3%)	25 (28.7%)	15 (33.3%)	52 (53.1%)	21 (43.8%)
Vomiting	0	1 (2.1%)	41 (41.8%)	11 (22.9%)	25 (28.7%)	7 (15.6%)	52 (53.1%)	15 (31.3%)
Urticaria	6 (6.1%)	2 (4.2%)	41 (41.8%)	21 (43.8%)	25 (28.7%)	14 (31.1%)	51 (52.0%)	24 (50.0%)
Pyrexia	0	0	40 (40.8%)	19 (39.6%)	23 (26.4%)	10 (22.2%)	50 (51.0%)	20 (41.7%)
Rhinorrhoea	3 (3.1%)	3 (6.3%)	29 (29.6%)	11 (22.9%)	15 (17.2%)	6 (13.3%)	42 (42.9%)	15 (31.3%)
Upper respiratory tract infection	0	2 (4.2%)	24 (24.5%)	10 (20.8%)	20 (23.0%)	8 (17.8%)	35 (35.7%)	13 (27.1%)
Diarrhoea	2 (2.0%)	1 (2.1%)	31 (31.6%)	11 (22.9%)	10 (11.5%)	3 (6.7%)	34 (34.7%)	13 (27.1%)
Erythema	2 (2.0%)	2 (4.2%)	29 (29.6%)	14 (29.2%)	10 (11.5%)	8 (17.8%)	34 (34.7%)	17 (35.4%)
Nasopharyngitis	1 (1.0%)	0	19 (19.4%)	11 (22.9%)	12 (13.8%)	6 (13.3%)	28 (28.6%)	13 (27.1%)
Pruritus	2 (2.0%)	0	22 (22.4%)	13 (27.1%)	8 (9.2%)	6 (13.3%)	27 (27.6%)	15 (31.3%)
Eczema	0	0	21 (21.4%)	12 (25.0%)	8 (9.2%)	3 (6.7%)	24 (24.5%)	12 (25.0%)
Abdominal pain	0	1 (2.1%)	21 (21.4%)	5 (10.4%)	7 (8.0%)	3 (6.7%)	23 (23.5%)	6 (12.5%)
Rash	0	0	17 (17.3%)	10 (20.8%)	9 (10.3%)	4 (8.9%)	23 (23.5%)	11 (22.9%)
Sneezing	4 (4.1%)	0	19 (19.4%)	7 (14.6%)	4 (4.6%)	3 (6.7%)	23 (23.5%)	9 (18.8%)
Rhinitis	0	1 (2.1%)	15 (15.3%)	5 (10.4%)	11 (12.6%)	3 (6.7%)	20 (20.4%)	8 (16.7%)
Perioral dermatitis	1 (1.0%)	0	11 (11.2%)	1 (2.1%)	7 (8.0%)	3 (6.7%)	17 (17.3%)	4 (8.3%)
Abdominal pain upper	1 (1.0%)	0	10 (10.2%)	2 (4.2%)	4 (4.6%)	2 (4.4%)	14 (14.3%)	4 (8.3%)
Nasal congestion	4 (4.1%)	0	9 (9.2%)	4 (8.3%)	2 (2.3%)	1 (2.2%)	14 (14.3%)	5 (10.4%)
Wheezing	0	0	11 (11.2%)	4 (8.3%)	4 (4.6%)	1 (2.2%)	14 (14.3%)	4 (8.3%)
Asthma	0	0	9 (9.2%)	2 (4.2%)	5 (5.7%)	5 (11.1%)	11 (11.2%)	7 (14.6%)
Constipation	0	0	8 (8.2%)	5 (10.4%)	3 (3.4%)	0	11 (11.2%)	5 (10.4%)
Ear infection	0	0	6 (6.1%)	2 (4.2%)	5 (5.7%)	0	11 (11.2%)	2 (4.2%)
Gastroenteritis	0	0	5 (5.1%)	4 (8.3%)	5 (5.7%)	3 (6.7%)	10 (10.2%)	6 (12.5%)
Headache	0	0	8 (8.2%)	1 (2.1%)	4 (4.6%)	0	10 (10.2%)	1 (2.1%)
Oral pruritus	0	0	7 (7.1%)	2 (4.2%)	4 (4.6%)	0	10 (10.2%)	2 (4.2%)
Teething	1 (1.0%)	0	8 (8.2%)	7 (14.6%)	1 (1.1%)	0	10 (10.2%)	7 (14.6%)

Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Eye pruritus	1 (1.0%)	0	5 (5.1%)	4 (8.3%)	4 (4.6%)	1 (2.2%)	9 (9.2%)	5 (10.4%)
Eye swelling	0	0	6 (6.1%)	3 (6.3%)	3 (3.4%)	0	9 (9.2%)	3 (6.3%)
Viral infection	0	0	6 (6.1%)	3 (6.3%)	5 (5.7%)	3 (6.7%)	9 (9.2%)	5 (10.4%)
Viral upper respiratory tract infection	0	0	7 (7.1%)	4 (8.3%)	4 (4.6%)	2 (4.4%)	9 (9.2%)	5 (10.4%)
Anaphylactic reaction [1]	0	0	2 (2.0%)	2 (4.2%)	6 (6.9%)	2 (4.4%)	8 (8.2%)	4 (8.3%)
Dry skin	0	0	6 (6.1%)	0	2 (2.3%)	2 (4.4%)	8 (8.2%)	2 (4.2%)
Gastroenteritis viral	0	0	6 (6.1%)	0	4 (4.6%)	1 (2.2%)	8 (8.2%)	1 (2.1%)
Rash erythematous	1 (1.0%)	0	7 (7.1%)	3 (6.3%)	1 (1.1%)	0	8 (8.2%)	3 (6.3%)
Throat irritation	1 (1.0%)	1 (2.1%)	6 (6.1%)	1 (2.1%)	4 (4.6%)	0	8 (8.2%)	2 (4.2%)
Arthropod bite	0	0	6 (6.1%)	1 (2.1%)	2 (2.3%)	1 (2.2%)	7 (7.1%)	2 (4.2%)
Conjunctivitis	0	0	4 (4.1%)	3 (6.3%)	2 (2.3%)	2 (4.4%)	6 (6.1%)	5 (10.4%)
Corona virus infection	0	0	1 (1.0%)	2 (4.2%)	5 (5.7%)	4 (8.9%)	6 (6.1%)	6 (12.5%)
Dermatitis atopic	0	0	5 (5.1%)	4 (8.3%)	1 (1.1%)	1 (2.2%)	6 (6.1%)	5 (10.4%)
Head injury	0	0	5 (5.1%)	1 (2.1%)	1 (1.1%)	0	6 (6.1%)	1 (2.1%)
Irritability	1 (1.0%)	0	6 (6.1%)	0	2 (2.3%)	1 (2.2%)	6 (6.1%)	1 (2.1%)
No adverse event	0	0	5 (5.1%)	1 (2.1%)	2 (2.3%)	0	6 (6.1%)	1 (2.1%)
Ocular hyperaemia	1 (1.0%)	0	4 (4.1%)	2 (4.2%)	3 (3.4%)	0	6 (6.1%)	2 (4.2%)
Contusion	2 (2.0%)	0	2 (2.0%)	0	2 (2.3%)	0	5 (5.1%)	0
Decreased appetite	0	0	3 (3.1%)	0	2 (2.3%)	0	5 (5.1%)	0
Dysphonia	0	0	3 (3.1%)	1 (2.1%)	3 (3.4%)	0	5 (5.1%)	1 (2.1%)
Ear pain	0	0	5 (5.1%)	3 (6.3%)	0	0	5 (5.1%)	3 (6.3%)
Flatulence	0	0	4 (4.1%)	0	1 (1.1%)	0	5 (5.1%)	0
Hand-foot-and-mouth disease	0	0	3 (3.1%)	0	2 (2.3%)	2 (4.4%)	5 (5.1%)	2 (4.2%)
Influenza	0	0	2 (2.0%)	0	3 (3.4%)	0	5 (5.1%)	0
Lip swelling	0	0	2 (2.0%)	0	3 (3.4%)	0	5 (5.1%)	0
Lower respiratory tract infection	0	0	5 (5.1%)	0	0	0	5 (5.1%)	0
Nausea	1 (1.0%)	0	4 (4.1%)	2 (4.2%)	1 (1.1%)	0	5 (5.1%)	2 (4.2%)
Rhinitis allergic	0	0	3 (3.1%)	0	3 (3.4%)	1 (2.2%)	5 (5.1%)	1 (2.1%)
Swelling face	0	0	5 (5.1%)	0	0	1 (2.2%)	5 (5.1%)	1 (2.1%)
Urinary tract infection	0	0	4 (4.1%)	0	2 (2.3%)	0	5 (5.1%)	0

Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Otitis media	0	0	2 (2.0%)	5 (10.4%)	4 (4.6%)	2 (4.4%)	4 (4.1%)	7 (14.6%)
Seasonal allergy	0	0	3 (3.1%)	4 (8.3%)	1 (1.1%)	1 (2.2%)	4 (4.1%)	4 (8.3%)
Papule	0	0	3 (3.1%)	3 (6.3%)	0	0	3 (3.1%)	3 (6.3%)
Rash macular	0	0	2 (2.0%)	3 (6.3%)	1 (1.1%)	1 (2.2%)	3 (3.1%)	4 (8.3%)
Bronchitis	0	0	2 (2.0%)	1 (2.1%)	0	2 (4.4%)	2 (2.0%)	3 (6.3%)
Epistaxis	0	0	0	3 (6.3%)	1 (1.1%)	1 (2.2%)	1 (1.0%)	3 (6.3%)
Respiratory syncytial virus infection	0	0	0	1 (2.1%)	0	2 (4.4%)	0	3 (6.3%)

At each level of summarization (any event and preferred term), subjects with more than 1 adverse event were counted only once within each study period. Shaded cells indicate adverse events and symptoms with ≥ 5% higher incidence in the AR101 group compared with the placebo group.

[1] None of the reported reactions were classified as severe.

CSR, Clinical Study Report.

Treatment-Related Adverse Events by Preferred Term

The only frequent treatment-related adverse event (≥ 20% of subjects in either treatment group) with ≥ 5% higher incidence in the AR101 group than the placebo group was cough, and the incidence of cough decreased substantially from up-dosing to maintenance.

Table 20: Treatment-related adverse events in at least 5% of subjects in either treatment group overall by system organ class and preferred term (safety population)

System Organ Class Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with at least 1 adverse event	15 (15.3%)	3 (6.3%)	67 (68.4%)	27 (56.3%)	30 (34.5%)	7 (15.6%)	74 (75.5%)	28 (58.3%)
Skin and subcutaneous tissue disorders	7 (7.1%)	3 (6.3%)	46 (46.9%)	18 (37.5%)	15 (17.2%)	3 (6.7%)	48 (49.0%)	18 (37.5%)
Urticaria	5 (5.1%)	1 (2.1%)	26 (26.5%)	13 (27.1%)	9 (10.3%)	2 (4.4%)	30 (30.6%)	14 (29.2%)
Erythema	1 (1.0%)	2 (4.2%)	17 (17.3%)	8 (16.7%)	4 (4.6%)	1 (2.2%)	19 (19.4%)	8 (16.7%)
Pruritus	2 (2.0%)	0	10 (10.2%)	10 (20.8%)	0	1 (2.2%)	11 (11.2%)	10 (20.8%)
Perioral dermatitis	1 (1.0%)	0	6 (6.1%)	0	4 (4.6%)	0	9 (9.2%)	0
Rash	0	0	5 (5.1%)	3 (6.3%)	2 (2.3%)	0	7 (7.1%)	3 (6.3%)
Eczema	0	0	5 (5.1%)	0	1 (1.1%)	0	5 (5.1%)	0
Rash erythematous	1 (1.0%)	0	3 (3.1%)	3 (6.3%)	0	0	3 (3.1%)	3 (6.3%)
Gastrointestinal disorders	3 (3.1%)	2 (4.2%)	33 (33.7%)	8 (16.7%)	18 (20.7%)	1 (2.2%)	45 (45.9%)	10 (20.8%)
Abdominal pain	0	1 (2.1%)	12 (12.2%)	2 (4.2%)	5 (5.7%)	0	15 (15.3%)	3 (6.3%)
Vomiting	0	0	12 (12.2%)	0	4 (4.6%)	0	15 (15.3%)	0
Diarrhoea	1 (1.0%)	1 (2.1%)	9 (9.2%)	4 (8.3%)	3 (3.4%)	0	11 (11.2%)	4 (8.3%)
Oral pruritus	0	0	4 (4.1%)	1 (2.1%)	4 (4.6%)	0	7 (7.1%)	1 (2.1%)
Respiratory, thoracic and mediastinal disorders	9 (9.2%)	2 (4.2%)	30 (30.6%)	9 (18.8%)	9 (10.3%)	2 (4.4%)	34 (34.7%)	12 (25.0%)
Cough	2 (2.0%)	0	17 (17.3%)	2 (4.2%)	4 (4.6%)	0	20 (20.4%)	2 (4.2%)
Sneezing	4 (4.1%)	0	14 (14.3%)	5 (10.4%)	2 (2.3%)	2 (4.4%)	16 (16.3%)	7 (14.6%)
Rhinorrhoea	3 (3.1%)	1 (2.1%)	9 (9.2%)	1 (2.1%)	4 (4.6%)	0	14 (14.3%)	2 (4.2%)
Nasal congestion	4 (4.1%)	0	3 (3.1%)	0	0	0	6 (6.1%)	0
Throat irritation	1 (1.0%)	1 (2.1%)	4 (4.1%)	1 (2.1%)	3 (3.4%)	0	5 (5.1%)	2 (4.2%)
Wheezing	0	0	4 (4.1%)	1 (2.1%)	1 (1.1%)	0	5 (5.1%)	1 (2.1%)

Source: Table 14.3.1.9

At each level of summarization (any event, system organ class, preferred term), subjects with more than 1 adverse event related to study product were counted only once within each study period. Shaded cells indicate adverse events with ≥ 5% higher incidence in the AR101 group compared with the placebo group.

The most frequent exposure-adjusted treatment-related adverse event rates overall were sneezing (1.49 events per subject-year AR101, 0.21 placebo), urticaria (1.05 events per subject-year AR101, 0.78 placebo), cough (0.70 AR101, 0.06 placebo), pruritus (0.16 AR101, 0.44 placebo), erythema (0.42 each AR101 and placebo), and diarrhea (0.38 AR101, 0.25 placebo).

When adjusted for exposure, the most frequent treatment-related adverse event rate with a difference between groups of ≥ 0.5 events per subject-year was sneezing with a difference in event rate between AR101 and placebo of 1.28 events per subject-year, followed by cough (difference 0.64), and the event rates decreased substantially from up-dosing to maintenance. All other adverse events had a difference between groups of less than 0.3 events per subject-year.

Table 21: Exposure-Adjusted Event Rates for the Most Frequent (≥ 5% Overall) Treatment-Related Adverse Events by Preferred Term in Study ARC005 (Safety Population, 1 to 3 Years)

Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98) (SYE = 0.55)	Placebo (N = 48) (SYE = 0.26)	AR101 (N = 98) (SYE = 51.71)	Placebo (N = 48) (SYE = 26.87)	AR101 (N = 87) (SYE = 46.16)	Placebo (N = 45) (SYE = 25.25)	AR101 (N = 98) (SYE = 98.42)	Placebo (N = 48) (SYE = 52.38)
Sneezing	4 (7.23)	0	141 (2.73)	8 (0.30)	2 (0.04)	3 (0.12)	147 (1.49)	11 (0.21)
Urticaria	6 (10.85)	1 (3.80)	76 (1.47)	37 (1.38)	21 (0.45)	3 (0.12)	103 (1.05)	41 (0.78)
Cough	2 (3.62)	0	51 (0.99)	3 (0.11)	16 (0.35)	0	69 (0.70)	3 (0.06)
Erythema	1 (1.81)	2 (7.61)	35 (0.68)	19 (0.71)	5 (0.11)	1 (0.04)	41 (0.42)	22 (0.42)
Abdominal pain	0	1 (3.80)	18 (0.35)	5 (0.19)	20 (0.43)	0	38 (0.39)	6 (0.11)
Diarrhoea	1 (1.81)	1 (3.80)	33 (0.64)	12 (0.45)	3 (0.06)	0	37 (0.38)	13 (0.25)
Rhinorrhoea	3 (5.42)	1 (3.80)	26 (0.50)	4 (0.15)	4 (0.09)	0	33 (0.34)	5 (0.10)
Vomiting	0	0	19 (0.37)	0	4 (0.09)	0	23 (0.23)	0
Pruritus	2 (3.62)	0	14 (0.27)	22 (0.82)	0	1 (0.04)	16 (0.16)	23 (0.44)
Oral pruritus	0	0	4 (0.08)	1 (0.04)	11 (0.24)	0	15 (0.15)	1 (0.02)
Perioral dermatitis	2 (3.62)	0	7 (0.14)	0	5 (0.11)	0	14 (0.14)	0
Rash	0	0	6 (0.12)	5 (0.19)	2 (0.04)	0	8 (0.08)	5 (0.10)

Number of total events and exposure adjusted event rates are presented. 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. Shaded cells indicate events with a difference of at least 0.5 events per subject-year between AR101 over placebo.

CSR, Clinical Study Report; SYE, subject-years of exposure.

Overall incidence of treatment-related AEs from the following studies: ARC003, ARC004, ARC005, ARC007, ARC010 and ARC011

The Criteria used for the selection of adverse reactions (ADRs) were the same for both age groups (1-3 and 4-17yrs). As such, the selection Criteria involved listing only those adverse reactions with a >5% absolute difference between AR101 and placebo at any dosing period from the treatment-emergent adverse events (AEs).

Table 22 represents the incidence of TEAEs by age group and overall.

Table 22: Adverse Reactions: Incidence of Treatment-related TEAEs by Age Group and Overall

System organ class Preferred term	Treatment-related TEAE		
	4-17 years	1-3 years	1-17 years
	ISS Integrated population[1]	ARC005 Safety Population[2]	Total[3]
	N=944 n (%)	N=98 n (%)	N=1042 n (%)
Immune system disorders	-	-	-
Anaphylactic reaction (systemic allergic reaction; any severity)	132 (14.0)	2 (2.0)	134 (12.9)
Anaphylactic reaction, severe (anaphylaxis; systemic allergic reaction, severe)	10 (1.1)	0 (0.0)	10 (1.0)
Respiratory, thoracic, and mediastinal disorders	-	-	-
Throat tightness	132 (14.0)	0 (0.0)	132 (12.7)
Cough	208 (22.0)	20 (20.4)	228 (21.9)
Sneezing	175 (18.5)	16 (16.3)	191 (18.3)
Throat irritation	391 (41.4)	5 (5.1)	396 (38.0)
Rhinorrhoea	126 (13.3)	14 (14.3)	140 (13.4)
Nasal congestion	106 (11.2)	6 (6.1)	112 (10.7)
Dyspnoea	76 (8.1)	1 (1.0)	77 (7.4)
Wheezing	89 (9.4)	5 (5.1)	94 (9.0)
Gastrointestinal disorders	-	-	-
Vomiting	269 (28.5)	15 (15.3)	284 (27.3)
Abdominal pain	467 (49.5)	15 (15.3)	482 (46.3)
Abdominal pain upper	216 (22.9)	4 (4.1)	220 (21.1)
Nausea	314 (33.3)	2 (2.0)	316 (30.3)
Abdominal discomfort	215 (22.8)	3 (3.1)	218 (20.9)
Paraesthesia oral	164 (17.4)	0 (0.0)	164 (15.7)
Oral pruritus	245 (26.0)	7 (7.1)	252 (24.2)
Lip pruritus	99 (10.5)	2 (2.0)	101 (9.7)
Eosinophilic oesophagitis	3 (0.3)	0 (0.0)	3 (0.3)
Skin and subcutaneous tissue disorders	-	-	-
Urticaria	271 (28.7)	30 (30.6)	301 (28.9)
Pruritus	320 (33.9)	11 (11.2)	331 (31.8)
Eczema	18 (1.9)	5 (5.1)	23 (2.2)
Perioral dermatitis	0 (0.0)	9 (9.2)	9 (0.9)

[1] Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.
[2] Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.
[3] The number of subjects with treatment-related TEAEs in the ISS integrated population and the ARC005 safety population were summed and the incidence manually calculated using the combined populations (N=1042) as the denominator.

Hypersensitivity Adverse Events

The most frequent exposure-adjusted hypersensitivity adverse event rates overall were urticaria (2.20 events per subject-year AR101, 1.57 placebo), sneezing (1.57 AR101, 0.15 placebo), erythema (0.61 AR101, 0.48 placebo), cough (0.69 AR101, 0.10 placebo), and pruritus (0.29 AR101, 0.36 placebo).

When adjusted for exposure, the most frequent hypersensitivity adverse event rate with a difference between groups of ≥ 0.5 events per subject-year was sneezing with a difference in event rate between AR101 and placebo of 1.42 events per subject-year, followed by urticaria (difference 0.63), and cough (0.59). The exposure-adjusted event rates for these adverse events decreased from up-dosing to

maintenance. All other adverse events had a difference between groups of less than 0.30 events per subject-year. Systemic allergic reaction (anaphylactic reaction) rates were similar between the AR101 (0.09 events per subject-year, 9 events) and placebo (0.08 events per subject-year, 4 events) groups.

Table 23: Exposure-Adjusted Event Rates for the Most Frequent (≥ 5% Overall) Treatment-Emergent Hypersensitivity Adverse Events by Preferred Term in Study ARC005 (Safety Population, 1 to 3 Years)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
Preferred Term	AR101 (N = 98) (SYE = 0.55)	Placebo (N = 48) (SYE = 0.26)	AR101 (N = 98) (SYE = 51.71)	Placebo (N = 48) (SYE = 26.87)	AR101 (N = 87) (SYE = 46.16)	Placebo (N = 45) (SYE = 25.25)	AR101 (N = 98) (SYE = 98.42)	Placebo (N = 48) (SYE = 52.38)
Urticaria	8 (14.47)	2 (7.61)	142 (2.75)	62 (2.31)	67 (1.45)	18 (0.71)	217 (2.20)	82 (1.57)
Sneezing	3 (5.42)	0	149 (2.88)	5 (0.19)	3 (0.06)	3 (0.12)	155 (1.57)	8 (0.15)
Cough	1 (1.81)	0	47 (0.91)	4 (0.15)	20 (0.43)	1 (0.04)	68 (0.69)	5 (0.10)
Erythema	1 (1.81)	0	45 (0.87)	19 (0.71)	14 (0.30)	6 (0.24)	60 (0.61)	25 (0.48)
Rhinorrhoea	2 (3.62)	1 (3.80)	27 (0.52)	4 (0.15)	6 (0.13)	0	35 (0.36)	5 (0.10)
Pruritus	2 (3.62)	0	23 (0.44)	15 (0.56)	4 (0.09)	4 (0.16)	29 (0.29)	19 (0.36)
Vomiting	0	0	21 (0.41)	1 (0.04)	5 (0.11)	0	26 (0.26)	1 (0.02)
Diarrhoea	0	1 (3.80)	24 (0.46)	10 (0.37)	1 (0.02)	0	25 (0.25)	11 (0.21)
Abdominal pain	0	0	16 (0.31)	6 (0.22)	7 (0.15)	1 (0.04)	23 (0.23)	7 (0.13)
Oral pruritus	0	0	8 (0.15)	3 (0.11)	11 (0.24)	0	19 (0.19)	3 (0.06)
Perioral dermatitis	2 (3.62)	0	9 (0.17)	2 (0.07)	8 (0.17)	0	19 (0.19)	2 (0.04)
Rash	0	0	10 (0.19)	5 (0.19)	4 (0.09)	3 (0.12)	14 (0.14)	8 (0.15)
Eye swelling	0	0	6 (0.12)	0	5 (0.11)	0	11 (0.11)	0
Anaphylactic reaction [1]	0	0	3 (0.06)	2 (0.07)	6 (0.13)	2 (0.08)	9 (0.09)	4 (0.08)
Eye pruritus	1 (1.81)	0	3 (0.06)	5 (0.19)	4 (0.09)	1 (0.04)	8 (0.08)	6 (0.11)

Summary includes all hypersensitivity events in ≥ 5% of subjects (safety population). Number of total events and exposure-adjusted event rates are presented. 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. Shaded cells indicate events with a difference of at least 0.5 events per subject-year between AR101 over placebo.

[1] None of the reported reactions were classified as severe.
CSR, Clinical Study Report; SYE, subject-years of exposure.

Serious adverse event / deaths / other significant events

Serious adverse event

Grade 3 and Higher Adverse Events

The 5-point CoFAR grading scale, 3-point EAACI grading scale, and 5-point CTCAE grading scale were used for coding the severity of adverse events. Grade 3 and higher (severe, life-threatening, and resulting in death) adverse events are described in this section. Five subjects (5.1%) in the AR101 group and 2 subjects (4.2%) in the placebo group had 1 or more grade 3 (severe) adverse events; none were considered to be related to the study product (Table 24).

Table 24: Treatment-Emergent Adverse Events of Grade ≥ 3 Severity by System Organ Class and Preferred Term in Study ARC005 (Safety Population, 1 to 3 Years)

System Organ Class Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 480	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with at least 1 adverse event	0	0	2 (2.0%)	0	3 (3.4%)	2 (4.4%)	5 (5.1%)	2 (4.2%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.0%)	0	3 (3.4%)	1 (2.2%)	4 (4.1%)	1 (2.1%)
Asthma	0	0	1 (1.0%)	0	1 (1.1%)	1 (2.2%)	2 (2.0%)	1 (2.1%)
Bronchial hyperreactivity	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Status asthmaticus	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Infections and infestations	0	0	2 (2.0%)	0	1 (1.1%)	0	3 (3.1%)	0
Enterovirus infection	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Respiratory syncytial virus bronchiolitis	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Upper respiratory tract infection	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Injury, poisoning and procedural complications	0	0	0	0	0	1 (2.2%)	0	1 (2.1%)
Carbon monoxide poisoning	0	0	0	0	0	1 (2.2%)	0	1 (2.1%)

CSR, Clinical Study Report.

Other Serious Adverse Events

Eight subjects experienced a total of 9 serious adverse events. The events were considered to be unrelated to study treatment. In the AR101 group, 1 subject each had an enterovirus infection, influenza, respiratory syncytial virus bronchiolitis, viral infection and status asthmaticus, and 2 subjects had asthma. In the placebo group, 1 subject each had asthma and carbon monoxide poisoning.

Table 25: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in Study ARC005 (Safety Population, 1 to 3 Years)

System Organ Class Preferred Term	Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with at least 1 adverse event	3 (3.1%)	0	3 (3.4%)	2 (4.4%)	6 (6.1%)	2 (4.2%)
Infections and infestations	2 (2.0%)	0	2 (2.3%)	0	4 (4.1%)	0
Enterovirus infection	1 (1.0%)	0	0	0	1 (1.0%)	0
Influenza	1 (1.0%)	0	0	0	1 (1.0%)	0
Respiratory syncytial virus bronchiolitis	0	0	1 (1.1%)	0	1 (1.0%)	0
Viral infection	0	0	1 (1.1%)	0	1 (1.0%)	0
Respiratory, thoracic and mediastinal disorders	1 (1.0%)	0	2 (2.3%)	1 (2.2%)	3 (3.1%)	1 (2.1%)
Asthma	1 (1.0%)	0	1 (1.1%)	1 (2.2%)	2 (2.0%)	1 (2.1%)
Status asthmaticus	0	0	1 (1.1%)	0	1 (1.0%)	0
Injury, poisoning and procedural complications	0	0	0	1 (2.2%)	0	1 (2.1%)
Carbon monoxide poisoning	0	0	0	1 (2.2%)	0	1 (2.1%)

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

CSR, Clinical Study Report

Maximum Severity of Symptoms During Dosing at the Study Site

Overall, 43.9% of AR101-treated subjects and 39.6% of placebo-treated subjects had allergy symptoms of any severity during dosing with study product at the study site. The maximum severity of symptoms was mild for 39.8% of subjects in the AR101 group and 39.6% of subjects in the placebo group and moderate for 4.1% of subjects in the AR101 group (no subjects in the placebo group had moderate symptoms). No subject died or had severe or life-threatening events due to allergy symptoms related to dosing at the study site.

Table 26: Maximum Severity of Symptoms During Study Product Dosing at the Study Site in Study ARC005 (Safety Population, 1 to 3 Years)

Dose Level		AR101 (N = 98)	Placebo (N = 48)
Overall	Subjects who received ≥ 1 dose	98	48
	Subjects with any symptoms related to dosing	43 (43.9%)	19 (39.6%)
	Maximum severity of any symptoms		
	None	55 (56.1%)	29 (60.4%)
	Mild	39 (39.8%)	19 (39.6%)
	Moderate	4 (4.1%)	0

Subjects were counted only once using the maximum severity of allergy symptoms per subject. Denominators for percentages were based on the number of subjects within each treatment group who received at least 1 dose at the corresponding dose level.

Deaths

No death or life-threatening events occurred in Study ARC005.

Adverse Events of Clinical Interest

Adverse events of clinical interest include systemic allergic reaction (including anaphylaxis), use of epinephrine (and associated adverse events), chronic or recurrent GI adverse events that led to permanent discontinuation of the study product (including EoE), and accidental food allergen exposure. Anaphylaxis and EoE are important identified risks of AR101 treatment as described in the risk management plan.

Systemic Allergic Reaction

Overall, 8 AR101-treated subjects (8.1%) and 4 placebo-treated subjects (8.3%) had 1 or more systemic allergic reactions. All events occurred during up-dosing and maintenance; none occurred during initial dose escalation; 2 subjects (2.0%) AR101 and 2 subjects (4.2%) placebo during up-dosing and 6 subjects (6.9%) AR101 and 2 subjects (4.4%) placebo during maintenance.

The 8 AR101-treated subjects experienced a total of 9 systemic allergic reactions (anaphylactic reactions) including 3 events triggered by study product, none by peanut or peanut-containing food, and 6 by other food allergen. In the placebo group, 4 subjects experienced 4 events of systemic allergic reaction, all triggered by other food allergen.

Overall, the maximum severity of systemic allergic reactions was mild for 2 subjects (2.0%) and moderate for 6 subjects (6.1%) in the AR101 group. The maximum severity was mild and moderate for 2 placebo subjects (4.2%) each. None of the systemic allergic reactions were severe or considered to be serious.

Epinephrine use was required for systemic allergic reactions in 5 AR101 subjects (5.1%) and 2 placebo subjects (4.2%).

Symptoms associated with systemic allergic reactions in the AR101 group were cough and urticaria (4 subjects each, 4.1%), throat irritation and wheezing (3 subjects each, 3.1%) and vomiting in 1 subject (1.0%). The subjects in the placebo group with systemic allergic reactions had associated symptoms of vomiting (3 subjects, 6.3%), cough (2 subjects, 4.2%), urticaria and wheezing, in 1 subject (2.1%) each.

Table 27: Summary of Treatment-Emergent Systemic Allergic Reaction (MedDRA Preferred Term Anaphylactic Reaction) Episodes by Study Period in Study ARC005 (Safety Population, 1 to 3 Years)

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with an anaphylactic reaction								
1 event	0	0	1 (1.0%)	2 (4.2%)	6 (6.9%)	2 (4.4%)	7 (7.1%)	4 (8.3%)
2 events	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
3 events	0	0	0	0	0	0	0	0
> 3 events	0	0	0	0	0	0	0	0
Subjects with an anaphylactic reaction by maximum severity [1]								
Mild	0	0	0	1 (2.1%)	2 (2.3%)	1 (2.2%)	2 (2.0%)	2 (4.2%)
Moderate	0	0	2 (2.0%)	1 (2.1%)	4 (4.6%)	1 (2.2%)	6 (6.1%)	2 (4.2%)
Severe	0	0	0	0	0	0	0	0
Subjects with a serious anaphylactic reaction	0	0	0	0	0	0	0	0
Subjects with an anaphylactic reaction requiring epinephrine use	0	0	1 (1.0%)	1 (2.1%)	4 (4.6%)	1 (2.2%)	5 (5.1%)	2 (4.2%)
Subjects with an anaphylactic reaction requiring epinephrine use by location of epinephrine use								
Location other than study site	0	0	1 (1.0%)	1 (2.1%)	3 (3.4%)	0	4 (4.1%)	1 (2.1%)
Study site	0	0	0	0	1 (1.1%)	1 (2.2%)	1 (1.0%)	1 (2.1%)
Number of anaphylactic reactions	0	0	3	2	6	2	9	4
Number of anaphylactic reactions by trigger								
Study product	0	0	3	0	0	0	3	0
Peanut or peanut containing food	0	0	0	0	0	0	0	0

	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Other food allergen	0	0	0	2	6	2	6	4
Other	0	0	0	0	0	0	0	0
Subjects with an anaphylactic reaction involving individual symptoms [2]								
Cough	0	0	0	0	4 (4.6%)	2 (4.4%)	4 (4.1%)	2 (4.2%)
Urticaria	0	0	0	0	4 (4.6%)	1 (2.2%)	4 (4.1%)	1 (2.1%)
Throat irritation	0	0	1 (1.0%)	0	2 (2.3%)	0	3 (3.1%)	0
Wheezing	0	0	2 (2.0%)	0	1 (1.1%)	1 (2.2%)	3 (3.1%)	1 (2.1%)
Vomiting	0	0	0	2 (4.2%)	1 (1.1%)	1 (2.2%)	1 (1.0%)	3 (6.3%)

[1] Severity was graded on a 3 point scale (mild, moderate, severe) according to the EAACI grading system (adapted from Muraro, 2007). None of the reported reactions were classified as severe.

[2] In at least 2 subjects overall in either treatment group.

CSR, Clinical Study Report; EAACI, European Academy of Allergy and Clinical Immunology.

Use of epinephrine

Epinephrine use was summarised by episode, defined as an administration of 1 or more epinephrine doses within 2 hours. The 2-hour window is clinically appropriate to document the use of epinephrine during an event and allowed for the collection of both biphasic responses and multiple events within individuals by time in the AR101 clinical studies.

In the safety population overall, 11 subjects (11.2%) in the AR101 group and 2 subjects (4.2%) in the placebo group had at least 1 episode of epinephrine use. No subject had more than 3 episodes of epinephrine use. One dose of epinephrine was administered for most episodes. Three events (in 2 subjects, 2.1%) in the AR101 group were considered related to study product.

Most episodes of epinephrine use were associated with mild or moderate adverse events; 2 events in the AR101 group and 1 event in the placebo group were severe. None of the severe reactions treated with epinephrine were related to study treatment.

Two events associated with the use of epinephrine in the AR101 group and 1 event in the placebo group were serious. None of the serious reactions treated with epinephrine were related to study treatment. None of the serious events associated with epinephrine use were allergic in nature. The serious events were respiratory syncytial virus bronchiolitis/status asthmaticus and asthma in the AR101 group and carbon monoxide poisoning in the placebo group.

In the AR101 group, epinephrine was used for treatment-related adverse events for 3 episodes (3%), 1 of which was a systemic allergic reaction (anaphylactic reaction); none of the events were severe or serious. Epinephrine was used in 10 episodes for accidental food allergen exposures in the AR101 group. Overall, most epinephrine use was at a location other than the study site (84.6% AR101, 75.0% placebo).

Chronic/Recurrent Gastrointestinal Adverse Events, EoE

In toddlers aged 1 to 3 years, Chronic or recurrent GI adverse events led to discontinuation of study product in 3 AR101-treated subjects (3.1%; 1 during up-dosing and 2 during maintenance); the events were regurgitation during up-dosing and abdominal discomfort and eructation during maintenance. No subjects in the placebo group discontinued due to chronic or recurrent GI adverse events.

Eosinophilic Esophagitis

In toddlers aged 1 to 3 years, EoE was not diagnosed in any subject in either treatment group.

In children 4-17 years of age, 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. Outside of the integrated safety population, 7 additional subjects had a diagnosis of EoE: 2 subjects in the phase 2 studies ARC001 (1 subject) and ARC002 (1 subject), 1 adult subject in study ARC004, and 4 subjects in study ARC008.

According to submitted data, the severity of EoE was considered mild in 2 subjects, moderate in 2 subjects, and severe in 1 subject. All 5 subjects with EoE discontinued the study, including 1 who was discontinued due to no longer meeting eligibility criteria. Outside of the integrated safety population, 7 additional subjects had a diagnosis of EoE: 2 subjects in the phase 2 studies ARC001 (1 subject) and ARC002 (1 subject), 1 adult subject in study ARC004, and 4 subjects in study ARC008. Clinical review of all the cases of EoE indicated that the onset of clinical symptoms was typically with dysphagia, vomiting, or both. The diagnosis of EoE was confirmed by esophagogastroduodenoscopy in all but one case, which was diagnosed based on clinical features. Most subjects were discontinued from AR101

treatment and treated with a proton pump inhibitor with or without a topical corticosteroid; all but 1 subject reported symptomatic improvement. Nearly all cases remain ongoing.

Study ARC007 evaluated the time to resolution of chronic or recurrent GI adverse events leading to study discontinuation after the last dose of study product and found that the time to resolution was within 2 weeks for 17 of 20 subjects, between 2 and 4 weeks in 2 subjects, and unknown for 1 subject. The most common GI adverse event during follow-up was abdominal pain.

Accidental Food Allergen Exposure

A total of 35 AR101-treated subjects had 70 accidental food allergen exposures and 22 placebo-treated subjects had 42 accidental food allergen exposures, with most subjects having 1 exposure (54.3% AR101, 50.0% placebo). A larger proportion of subjects reported accidental exposures during up-dosing than during maintenance. Most subjects had accidental exposures that were not peanut related.

No subject had an accidental food allergen exposure considered serious. Overall, most subjects required treatment for accidental exposures. Two AR101-treated subjects and 1 placebo-treated subject reported accidental exposures that required epinephrine use during up-dosing, and 3 AR101-treated subjects reported exposures that required epinephrine use during maintenance.

A total of 5 AR101-treated subjects had 7 peanut exposures, 2 of which required treatment. One AR101-treated subject had peanut exposure with no adverse event. A total of 3 placebo-treated subjects had 4 peanut exposures, 3 of which required treatment. No peanut exposures were associated with the use of epinephrine. All other exposures were non-peanut food allergens.

Laboratory findings

Hematology parameters were measured at baseline, end of up-dosing, and study exit in subjects.

The numbers of subjects with shifts in haematology parameters from baseline to worst postbaseline assessment was low overall. Minor differences were noted between treatment groups in the incidence of shifts from baseline to worst postbaseline assessment in a higher proportion of subjects in the AR101 group compared with the placebo group for WBC count (shift from normal to low), monocytes (shift from normal to low), and eosinophils (shift from normal to high).

No meaningful differences were observed between treatment groups in the change from baseline in any other hematology laboratory parameter

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

No potential drug or food interactions with AR101 are known. AR101 is intended to be taken with food, mixed in a soft food matrix for dosing.

Discontinuation due to adverse events

Six subjects in the AR101 group (6.1%) discontinued study product due to 1 or more adverse events. These subjects discontinued study product during up-dosing (4 subjects) or maintenance (2 subjects);

1 subject had an event during both up-dosing and maintenance that led to study product discontinuation during maintenance.

AR101 was discontinued due to an event in the GI disorders system organ class for five (5.1%) subjects; 1 (1.0%) subject each with abdominal discomfort, abdominal pain, eructation, regurgitation and vomiting and was discontinued due to an event in the respiratory, thoracic and mediastinal disorders system organ class for four (4.1%) subjects; 2 (2.0%) subjects with cough and 1 (1.0%) subject each with asthma and throat clearing.

No subjects in the placebo group discontinued study product due to an adverse event.

Table 28: Treatment-Emergent Adverse Events Leading to Discontinuation of Study Product by System Organ Class and Preferred Term (Safety Population, 1 to 3 Years)

System Organ Class Preferred Term	Initial Dose Escalation		Up-Dosing		Maintenance		Overall	
	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 98)	Placebo (N = 48)	AR101 (N = 87)	Placebo (N = 45)	AR101 (N = 98)	Placebo (N = 48)
Subjects with at least 1 adverse event	0	0	5 (5.1%)	0	2 (2.3%)	0	6 (6.1%)	0
Gastrointestinal disorders	0	0	3 (3.1%)	0	2 (2.3%)	0	5 (5.1%)	0
Abdominal discomfort	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Abdominal pain [1]	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Eructation	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0
Regurgitation	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Vomiting	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Respiratory, thoracic and mediastinal disorders	0	0	3 (3.1%)	0	1 (1.1%)	0	4 (4.1%)	0
Cough [2]	0	0	2 (2.0%)	0	0	0	2 (2.0%)	0
Asthma	0	0	1 (1.0%)	0	0	0	1 (1.0%)	0
Throat clearing	0	0	0	0	1 (1.1%)	0	1 (1.0%)	0

At each level of summarisation (any event, system organ class, and preferred term), subjects with more than 1 adverse event leading to discontinuation of study product were counted only once within each study period. The overall column excludes symptoms recorded during the exit double-blind, placebo-controlled food challenge.

[1] Action taken was study product permanently discontinued; however, primary reason for study discontinuation was subject withdrew consent.

[2] One subject had cough during up-dosing but discontinued study product during maintenance.

CSR, Clinical Study Report

Post marketing experience

AR101 is currently marketed as Palforzia in the European Union, Switzerland, the United Kingdom and the United States of America. It 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. Post marketing safety and efficacy data have been reviewed in the Periodic Safety Update Reports. Palforzia is not yet licensed for patients aged 1 to 3 years.

A search of the ARGUS global safety database through 01 August 2023 identified two spontaneous, non-serious cases in patients aged 1 to 3 years treated with Palforzia. The first case involved a 3-year-old female patient that developed pruritus and rash during the up-dosing phase. The events were considered related to Palforzia. The patient recovered and was able to continue the up-dosing cycle. The second case involved a 3-year-old male patient that developed illness during the up-dosing phase. The event was considered not related to the Palforzia. Based on these data, the adverse event profile appears similar to that observed in clinical trials and in older patients.

2.5.1. Discussion on clinical safety

The summary of clinical safety (SCS) for patients aged 4 to 17 years was derived from the 5 clinical studies involving 944 unique subjects aged 4 to 17 years who received at least 1 dose of AR101 study product (3 completed phase 3 studies, ARC003, ARC007 (North America only), and ARC010 (Europe only) and 2 previously ongoing follow-on studies, ARC004 and ARC011).

The safety data from the new phase 3 study, in children aged 1 to 3 years (ARC005), are not integrated in the SCS for patients aged 4 to 17 years. This “new” safety data with focus on children aged 1 to 3 years (ARC005) have been presented separately.

In Study ARC005, in the safety population, 83 of 98 (84.7%) subjects in the AR101 group and 45 of 48 (93.8%) subjects in the placebo group completed the study. The most common reasons for study discontinuation in the AR101 group were subject withdrew consent and adverse event (5 of 98 subjects [5.1%] each). Likewise, in subjects 4 – 17 years, adverse events had been the most common primary reason for study discontinuation with 9.0% (AR101) and 1.5% (placebo) in the controlled population (controlled population represented 841 subjects treated with AR101 and 335 subjects treated with placebo from the above mentioned SCS, of subjects aged 4 to 17 years), 9.0% (AR101) in the integrated safety population (of all AR101 treated subjects, n = 944), followed by withdrawal of consent (6.3%, 3.0%, 10.8%).

As outlined above, an imbalance was noted in the baseline characteristic of included subjects in terms of the sensitisation profile between treatment groups. Therefore, one may conclude that at the baseline DBPCFC participants in the placebo group seem to react at slightly lower doses at screening and their baseline median peanut-specific IgE and Ara h subtype IgE levels were numerically lower compared to subjects in the AR101 group. This imbalance might potentially affect outcome parameters like severity of reactions or the use of epinephrine.

The most common adverse events (≥ 20% of subjects in either treatment group overall with ≥ 5% higher incidence in the AR101 group) in decreasing order were cough, vomiting pyrexia, rhinorrhea, upper respiratory tract infection, diarrhea, and abdominal pain; the incidence of each decreased substantially from up-dosing to maintenance. When adjusted for exposure, the most frequent adverse event rate with the highest difference between groups of ≥ 0.5 events per subject-year was sneezing with difference in event rate between AR101 and placebo of 1.31 events per subject-year (AR101, 1.69 event per subject-year vs placebo, 0.38 events per subject-year). Other adverse events with a

difference between groups of ≥ 0.5 events per subject-year were cough (0.93) and vomiting (0.61). The exposure-adjusted event rates for all of these adverse events decreased substantially from up-dosing to maintenance.

Described common adverse events, like vomiting, rhinorrhea, cough, sneezing, diarrhea, or abdominal pain are described of being slightly more prominent in the AR101 treated group. These symptoms reflect those, which are described as being treatment related in the population of 4-17 years old as well.

In terms of treatment-related adverse events and hypersensitivity events, the most frequent exposure-adjusted hypersensitivity adverse event rates overall were urticaria (2.20 events per subject-year AR101, 1.57 placebo), sneezing (1.57 AR101, 0.15 placebo), erythema (0.61 AR101, 0.48 placebo), cough (0.69 AR101, 0.10 placebo), and pruritus (0.29 AR101, 0.36 placebo). Treatment-related adverse events in at least 10% of subjects in the AR101 group and at least 5% higher over the placebo group was cough (20.4% in ARC010), followed by abdominal pain (15.3%), vomiting (15.3%) and rhinorrhoea (14.3%). When adjusted for exposure, the most frequent treatment-related adverse event rate with a difference between groups of ≥ 0.5 events per subject-year was sneezing with a difference in event rate between AR101 and placebo of 1.28 events per subject-year, followed by cough (difference 0.64). The incidence of treatment-related and hypersensitivity adverse events decreased substantially from up-dosing to maintenance.

The Applicant used a Chi-squared test to determine statistically significant differences between AR101-treated and placebo-treated subjects for selection of ADRs to be included in the SmPC at the nominal level of $\alpha=0.1$. In addition to this statistical analysis, the Applicant provided further justifications in case AEs were not considered to be included in the PI despite observed differences between treatment groups. PT have been grouped, which was accepted after some requested revisions.

The majority of adverse events were mild or moderate in severity. The incidence of severe adverse events was low; 5.1% in the AR101 group and 4.2% in the placebo group. None of the severe events were considered to be related to the study product. No subject had an adverse event that was life-threatening or led to death.

Eight subjects (6 AR101, 6.1%; 2 placebo, 4.2%) experienced a total of 9 serious adverse events during the study. No serious adverse events were considered by investigators to be related to study treatment.

Six AR101-treated subjects (6.1%) discontinued from the study due to 1 or more adverse events; 5 (5.1%) during up-dosing and 2 (2.3%) during maintenance; 1 subject had an event during both up-dosing and maintenance that led to study product discontinuation during maintenance. No placebo-treated subjects discontinued from the study due to adverse events. The majority of adverse events were mild or moderate in severity. None of the severe events were considered by the investigators to be related to the study product. Fewer subjects discontinued due to adverse events in the toddlers' study compared to the older children (6.1% compared to 11.4%). The predominant reason for discontinuation in both age groups was GI events such as abdominal pain, nausea and vomiting.

In terms of systemic allergic reactions, including anaphylaxis, in the AR101 group, 8 subjects (8.2%) subjects had a total of 9 systemic allergic reactions (anaphylactic reactions of any severity), including 3 events (in 2 subjects, 2.0%) triggered by study product, none by peanut or peanut containing food, and 6 (6.1%) by other non-peanut food allergen exposure. In the placebo group, 4 (8.3%) subjects had 4 systemic allergic reactions, all 4 triggered by other food allergen. No events were severe. All events occurred during up-dosing and maintenance; none occurred during initial dose escalation. The most common associated symptoms in the AR101 group were cough and urticaria (4 subjects each, 4.1%), followed by throat irritation and wheezing (3 subjects each, 3.1%). In the placebo group, the

most common associated symptoms were vomiting (3 subjects, 6.3%) and cough (2 subjects, 4.2%).

Most episodes of epinephrine use were associated with mild or moderate adverse events; 2 events in the AR101 group and 1 event in the placebo group were severe. The majority of episodes of epinephrine use required a single dose. None of the severe reactions treated with epinephrine were related to study therapy. Two events associated with the use of epinephrine in the AR101 group (respiratory syncytial virus bronchiolitis/status asthmaticus and asthma) and 1 event in the placebo group (carbon monoxide poisoning) were serious. None of these were allergic in nature.

Eosinophilic oesophagitis (EoE) was not diagnosed in any subject in either treatment group in children aged 1-3 years in ARC005. According to the submitted documents, in 4 to 17-year olds EoE was diagnosed in 5 of 944 subjects (0.5% overall) in the controlled and integrated safety populations with a further 7 cases in other studies (1 subject in ARC001, 1 subject in ARC002, 1 adult subject in ARC004, and 4 subjects in ARC008) to total 12 of 1217 subjects (approximately 1%) treated with PALFORZIA experiencing EoE.

Cumulatively during the post-marketing period from 31 January 2020 to 30 January 2024, a total of 24 cases (7 serious) of EoE adverse drug reactions were reported.

Clinical review of all the cases of EoE indicated that the onset of clinical symptoms was typically with dysphagia, vomiting, or both.

In ARC005, a history of food protein-induced enterocolitis syndrome (FPIES) and - following the global amendment 1.0 - a history of failure to thrive are included in the exclusion criteria, as these could have affected the safety evaluation of Palforzia in the clinical trial.

FPIES is a type of non-IgE mediated GI disease that can present with severe vomiting, diarrhoea and dehydration. Like food allergies, FPIES reactions are triggered by eating a particular food. The most common triggers include cow milk, soy and grains (rice, barley, oats).

In recent years, cases of FPIES in infancy/early childhood are presented more often – either in the context of changed feeding recommendation (including an “early introduction of peanut”), or due to increased attention to this disorder. As such, the Applicant cited literature form Caubet 2015 and Rotella 2023 and stated: “s*cientific literature review did highlight a change in reporting of FPIES to peanut from before publication of 2017 guidelines recommending early peanut introduction in infancy and after adoption of these recommendations into clinical practice*”. Subsequently, due the high frequency of described GI associated symptoms like vomiting or abdominal discomfort, special warning and precaution for use have been updated in the section 4.4 of the SmPC on IgE- and non-IgE-mediated GI diseases in the context of AR1010 treatment. The current caution in the SmPC Section 4.4 for all ages to discontinue AR101 in cases of "persistent or severe gastrointestinal symptoms" was added with the recommendation that “For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups, or food refusal and failure to thrive especially assessed in toddlers and younger patients (ages 1 to 3 years), the potential for a diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE should be considered. Additionally, FPIES, a food-associated non-IgE mediated gastrointestinal disease that may occur in toddlers, should be considered in any toddler with significant food associated GI symptoms.”

“A history of food protein-induced enterocolitis syndrome (FPIES)” and “A history of failure to thrive” were also included as contraindication in the product information.

The incidence of reported accidental exposure to any food allergen was lower in the AR101 group. A total of 35 subjects (35.7%) in the AR101 group had 70 accidental food allergen exposures and 22 subjects (45.8%) in the placebo group had 42 accidental food allergen exposures, and most had 1 episode (19 subjects [54.3%] in AR101, and 11 subjects [50.0%] in placebo). All peanut-related

allergen exposures were accidental. A total of 5 AR101-treated subjects had 7 peanut exposures, 2 of which required treatment. One AR101-treated subject had a peanut exposure with no adverse event. A total of 3 placebo-treated subjects had 4 peanut exposures, 3 of which required treatment. No peanut exposures were associated with the use of epinephrine.

2.5.2. Conclusions on clinical safety

Safety data to support the proposed AR101 dosing regimen in subjects aged 1 to 3 years are provided for 98 subjects who received at least 1 dose of AR101 including 87 subjects who received the maintenance dose of 300 mg/day (ARC005). In the ARC005 study, no new safety concerns were identified. The overall observed pattern of adverse events in this study was consistent with the completed phase 2 and phase 3 studies of AR101 in older populations. The incidence of adverse events, including such classified as non-treatment-related, decreased substantially from up-dosing to maintenance. The predominant reason for study discontinuation in subjects aged 1 to 3 years as well as in older subjects aged 4 to 17 years, was GI events such as abdominal pain, nausea and vomiting.

Although, no cases of EoE were detected, especially in the younger age group, occurrence of GI events like vomiting, abdominal distress, and/or failure to thrive still imply the potential for the development of IgE- or non-IgE-mediated GI diseases, such as EoE or FPIES.

In the toddler's study, aged 1 to 3 years, no severe systemic allergic reactions (anaphylaxis) were seen. Whereas, anaphylaxis was reported in children aged 4 to 17 years in 10 subjects (1.1% overall), over time. Eight of the 10 subjects who experienced anaphylaxis had potential cofactors. The management with co-factors requires high compliance, as outlines in the product information. Thus, this compliance and shared-decision process is in general high in parents of little children, but gets less in older children, adolescents or young adults. Thus, this observation may also be associated with the importance of treatment adherence. Still, although generally the safety profile represents as being less severe in the younger age group with n = 98 AR101 treated children in ARC005, the occurrence of allergic reactions - including anaphylaxis - remain a constant companion.

In all, AR101 appeared to have an acceptable safety profile in this study, consistent with previous AR101 studies in older subjects aged 4 to 17 years. No new safety concerns were identified in the younger population.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 1.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Table 29: Summary of safety concerns

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

Pharmacovigilance plan

Table 30: Ongoing and planned additional pharmacovigilance activities

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

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

Risk minimisation measures

Table 31: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
(Missing information)	Additional risk minimisation measures: • *None*	• *None* Additional pharmacovigilance activities: • *Study ARC008 extension*

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 5.1, 6.5 and 8 of the SmPC have been updated to add information on the age group of 1 to 3 years old children. The indication is extended to include the treatment of patients 1 to 3 years old for PALFORZIA based on final results from study ARC005; this is a Phase 3 randomised, double-blind, placebo-controlled Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (POSEIDON) to evaluate the safety and efficacy of peanut powder in terms of superiority of placebo in children of 1 year to less than 4 years of age with peanut allergy. The Package Leaflet (PL) is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to update the list of local representatives in the Package Leaflet. As part of the application the MAH is requesting a 1-year extension of the market protection.

Furthermore, a new pack-size of 16 capsules of 1 mg (Level 0) in blisters for PALFORZIA, 1 mg, oral powder in capsules for opening is introduced for the up-dosing phase for patients 1 to 3 years old. Consequently modules 3.2.P.1 and 3.2.P.7 were updated. Labelling was updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update module 3.2.P.3.1 to take out the EU importation site (editorial change).

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.

2.7.2. 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 that was authorised after 1 January 2011.

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

The extension of indication applied for by the applicant is to include the treatment of Palforzia to patients aged 1 to 3 years old. The full indication is for the treatment of patients aged 1 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older.

The aim of the treatment is to desensitise patients with peanut allergy by gradually increasing the body's ability to tolerate small amounts of peanut.

3.1.2. Available therapies and unmet medical need

Standard of care include strict avoidance of peanut and treatment for allergic reactions following exposure. 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 (eg, antihistamines, epinephrine auto-injectors). Prompt treatment with intramuscular epinephrine is the first-line treatment for anaphylaxis (Muraro, 2007). However, exposure to peanut is unpredictable, and the risk of severe reactions increases when access to medical care and epinephrine are not readily available (Sampson, 2005).

Prior to the approval of Palforzia in children aged 4 to 17 years, no licensed therapeutic option was available for use in routine clinical practice for the treatment of people with peanut allergy. No pharmaceutical product is approved for 1 to 3 years old children, therefore there remains an unmet medical in this age group.

3.1.3. Main clinical studies

The efficacy and safety of Palforzia in peanut-allergic toddlers aged 1 to 3 years old was assessed in a randomised, double-blind, placebo-controlled, multicentre, phase 3 study (ARC005 – POSEIDON). The study was conducted in 14 sites in North America and 9 in Europe.

A total of 289 subjects were screened and 146 were randomly assigned (2:1) to study treatment (98 to PALFORZIA and 48 to placebo). The primary efficacy analysis population consisted of 98 subjects who received at least one dose of study treatment. In this study, eligible subjects were those sensitive to > 3 mg and ≤ 300 mg of peanut protein at the screening DBPCFC.

With regard to dosing regimen, after an initial dose escalation ranging from 0.5 mg to 3 mg on day 1 and confirmation of tolerability of 1 mg on day 2, subjects underwent up-dosing for 20-40 weeks starting at 1 mg until the 300 mg dose was reached. The up-dosing period was approximately 6 months (maximum 40 weeks), with dose escalation approximately every 2 weeks. As for study ARC003 (subjects aged 4 to 17 years), subjects who tolerated the 300 mg/day dose for 2 weeks within 40 weeks began the maintenance period and continued daily dosing with study product at 300 mg/day for an overall total of approximately 12 months of treatment.

The primary efficacy endpoint was the proportion of subjects who tolerated a single highest dose of at least 1 000 mg peanut protein with no more than mild allergic symptoms at the exit DBPCFC

(desensitisation response rate). Key secondary endpoints included determination of the desensitisation response rates after single doses of 300 mg and 600 mg peanut protein and the maximum severity of symptoms at the exit DBPCFC. In addition, the highest tolerated dose at the exit double-blind, placebo-controlled food challenge DBPCFC was included as a pre-specified exploratory endpoint.

After a total of approximately 1 year of blinded treatment, subjects completed an exit DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative, as an exploratory endpoint). Besides a few differences in the ARC005 study design such as different starting dose (1 mg for 1-3 years while 3 mg was used for 4-17 years, and length of the study (slightly longer) to up dose to a 300 mg highest dose before maintenance period, or higher endpoint challenge dose), all the other studies for 4 years and above were conducted with a similar design (Figure 1).

3.2. Favourable effects

The primary efficacy endpoint for study ARC005 was met. Treatment with Palforzia resulted in a statistically significant treatment effect over placebo in the proportion of toddlers aged 1 to 3 years who tolerated peanut protein with no more than mild symptoms at the exit DBPCFC after approximately 6 months of maintenance treatment. Of 98 subjects in the ITT population who received Palforzia, the desensitisation response rate to a single highest dose of at least 1000 mg peanut protein was 68.4% (95% CI: 58.2, 77.4) compared with 4.2% (95% CI: 0.5, 14.3) for the 48 subjects who received placebo; the treatment difference (Palforzia-placebo) was 64.2% (95% CI 47.0, 81.4; $p < 0.0001$).

The desensitisation response rates seen in study ARC005 were robust and consistent with previous clinical trials, with the toleration single dose of at least 1000 mg peanut protein showing numerically higher responses for toddlers aged 1 to 3 years treated with Palforzia (68.4%) than seen in the pivotal 4 to 17 years efficacy trials (rates of 50.3% and 58.3%, respectively, in studies ARC003 and ARC010).

The population used for the primary efficacy analyses in studies ARC003, ARC005, and ARC010 included subjects aged 1 to 17 years at screening who were sensitive to peanut and at risk for moderate to severe allergic reactions following exposure to relatively small amounts of peanut protein, ≤ 300 mg peanut protein in the screening DBPCFC. The maintenance dose in all studies was 300 mg peanut protein. Considering a dose of 300 mg peanut protein being equivalent to about one peanut kernel, 1000 mg represent approximately 3 to 4 peanut kernels. 1000 mg is an amount being generally higher than an unintended exposure to peanut protein. Thus, this increase in threshold reactivity is considered clinical meaningful.

Palforzia treatment resulted in decreased clinical reactivity to peanut protein and also in a statistically significant treatment effect over placebo in reducing the maximum severity of symptoms at any challenge dose during the exit DBPCFC for subjects aged 1 to 17 years in the ITT populations of ARC003, ARC005, and ARC010. In ARC005, the maximum severity of symptoms was no symptoms (51.0% Palforzia, 4.2% placebo), mild symptoms (29.6%, 47.9%), moderate symptoms (17.3%, 43.8%), and severe symptoms (2.0%, 4.2%). 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%). Data gained in ARC003 were comparable to ARC010. 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. Of the subjects who used epinephrine at the screening peanut DBPCFC, 15.9% of subjects treated with Palforzia compared with 81.4% of subjects treated with placebo used epinephrine as rescue medication during the exit DBPCFC in ARC003, 7.2% of subjects treated with Palforzia compared with 37.8% of subjects treated with placebo used epinephrine as rescue medication during

the exit DBPCFC in ARC005, and no Palforzia-treated subjects compared with 62.5% of placebo-treated subjects used epinephrine as rescue medication during the exit peanut DBPCFC in ARC010.

3.3. Uncertainties and limitations about favourable effects

The AR101 treatment resulted in statistically significant treatment effects over placebo, with treatment differences (AR101-placebo) of 47.8% ($p < 0.0001$) in ARC003, 56.0% ($p < 0.0001$) in ARC010, and 64.2% in ARC005. However, in ARC005 an imbalance in baseline parameters such as the median peanut-specific IgE and Ara h2 compared with the placebo group was noted (median peanut-specific IgE and Ara h 2 IgE numerically lower in the AR101 group (6.8 kUA/L and 5.190 kUA/L, respectively) compared with the placebo group (30.0 kUA/L and 14.200 kUA/L)) and could have influenced this treatment difference. Consequently, it was elucidated further if and to which extent observed imbalance may potentially influence the treatment effect. An updated analysis controlling for the multiple baseline variables (ps-IgE, ps-IgE/IgG4 ratio, Ara h 1 IgE, Ara h 2 IgE, Ara h 3 IgE, Ara h 9 IgE, and Ara h 9 IgG4) was performed. Additional analyses showed that the baseline imbalance in in vitro sensitisation parameters did not substantially affect treatment effect estimates for the primary or relevant secondary study outcomes.

The extent of drug exposure for a number of ARC005 subjects due to the COVID-19 pandemic did not change the statistical significance of the analysis, as shown by additional controlling for age and total study drug exposure. However, as discussed in more detail above, some differences are noted in the treatment effect estimates in the various models. Whether age or exposure would be the driving factor cannot be satisfactorily evaluated. Nevertheless, since the effect estimates tend towards a higher effect (if affected) this is not further pursued. The MAH discussed the potential impact of protocol deviations. Data suggest that these did not have a major impact on study objectives, efficacy results or interpretation of study results.

AR101 needs to be taken daily, which is often associated with a great and persuading effort of patients and their families. Although under continuous treatment, continued peanut avoidance and carrying an epinephrine auto-injection device for emergency treatment is necessary. Thus, balancing the effort of daily consumption with the individual outcome in terms of possible limitation in quality of life, remain a constant process of shared decision making between the patient and their families as well as the treating physician. The younger the patient is, the more decisions are made by the parents. However, once considering the possible (life-)long treatment, the growing child / subsequent adolescent patient may develop another perspective than the parents. In consequence, the patients may put themselves at risk for (unexpected) allergic reactions including anaphylaxis by not continuing the daily treatment.

Currently, experiences are limited how treatment compliance over a longer time is transferable into daily live. Data of the open follow-up study ARC004, group 2, cohort 1, of about 100 subjects who completed the exit DBPCFC after a median overall exposure to AR101 of approximately 19 months (580.5 days; range, 388-761 days), showed that desensitization was maintained or improved in subjects aged 4 to 17 years. Study ARC008, a study included diverse subjects from various AR101 studies, spanning different age groups (1-3 years and 4-17 years), has evaluated safety and efficacy of longer-term exposure to AR101 for ≥ 5 years.

It is noted that although 300 mg daily dose of study product had to be tolerated for at least 2 consecutive weeks before having the DBPCFC, still several subjects did not tolerate 300 mg or less at the exit challenge – in the ITT population and even in the completer population. This means, that although these subjects tolerated their maintenance dose, they did not tolerate 300 mg during exit DBPCFC. The Applicant believes that these data represent false positive. For example, anxiety on the test day with associated flaring of eczema, urticaria, and/or subjective throat tightness could be

interpreted as evidence of a positive challenge. In addition, challenge results might had been true positives, reflecting an unexpected change in reaction threshold in terms of co-factors e.g. the presence of a viral upper respiratory infection or poor sleep.

The observation of these "fluctuating" individual reaction thresholds illustrates once again how carefully these results should be interpreted for the individual patient: the mg of protein peanut achieved in the challenge cannot be regarded as reaction thresholds set in stone.

Definitely, data from 98 subjects' age 1 to 3 years in the ITT population who received AR101, compared with 48 subjects in the placebo group, still represent a small data set, which hamper robust estimations in terms of specifying such further characteristics.

3.4. Unfavourable effects

In the toddler study, the overall incidence of adverse events of any severity and relationship to the Palforzia study product was high, about 98.0% in both groups. Still, the majority of adverse events were mild or moderate in severity. This result was not unexpected as allergic reactions or symptoms related to IgE-mediated hypersensitivity reactions are an expected consequence of the therapeutic process of gradual desensitisation to the allergen

The most common adverse reactions (of any severity) in patients aged 1 to 3 years old were urticaria (30.6%), cough (20.4%), erythema (19.4%), sneezing (16.3%), abdominal pain (15.3%), vomiting (15.3%), and rhinorrhoea (14.3%). The incidence of adverse reactions was higher during up-dosing (68.4%) than initial dose escalation (15.3 %) and maintenance (34.5 %). 6.1% of subjects discontinued study product due to 1 or more adverse reactions.

Gastrointestinal disorders were the most common reasons leading to discontinuation of treatment in 5 (5.1%) subjects: 1 (1.0%) subject each with abdominal discomfort, abdominal pain, eructation, regurgitation and vomiting.

For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia) in all age groups, or food refusal and failure to thrive especially assessed in toddlers and younger patients (ages 1 to 3 years), the potential for a diagnosis of IgE- or non-IgE-mediated gastrointestinal diseases such as EoE should be considered. Additionally, FPIES, a food-associated non-IgE mediated gastrointestinal disease that may occur in toddlers, should be considered in any toddler with significant food associated GI symptoms (see section 4.4 of the SmPC). A history of food protein-induced enterocolitis syndrome (FPIES) in the past 12 months (applicable for patients aged 1-3 years) and a history of failure to thrive (applicable for patients aged 1-3 years) are included as contra-indication in the product information.

Systemic allergic reactions of any severity were reported in 8.1% of subjects treated with Palforzia, including 0% during initial dose escalation, 2.0% during up-dosing, and 6.9% during maintenance. Out of the 9 total systemic allergic reactions, 3 were related to study drug. Among placebo-treated subjects, 8.3% experienced systemic allergic reactions. Of the Palforzia-treated population, 7% of subjects reported a single episode of systemic allergic reaction and 1% reported two or more systemic allergic reactions. The most commonly reported symptoms of systemic allergic reactions were cough and urticaria, followed by throat irritation and wheezing. No severe systemic allergic reactions (anaphylaxis) were reported in study ARC005.

Overall, in toddlers aged 1 to 3 years, no notable difference was seen in the occurrence of all-cause systemic allergic reactions between Palforzia (8.1%) and placebo (8.3%). The overall incidence of systemic reactions was lower than that seen in children aged 4 to 17 years (15.1%).

Eosinophilic Esophagitis, EoE is identified as a known risk in the risk management plan. In toddlers, no case of EoE was identified. In 4 to 17-year olds 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. Clinical review of all the cases of EoE indicated that the onset of clinical symptoms was typically with dysphagia, vomiting, or both. A further 7 cases had been identified in other studies (1 subject in ARC001, 1 subject in ARC002, 1 adult subject in ARC004, and 4 subjects in ARC008) leading to a total of 12 of 1217 subjects. Cumulatively during the post-marketing period from 31 January 2020 to 30 January 2024, a total of 24 cases (7 serious) of EoE adverse drug reactions were reported.

IgE-mediated hypersensitivity reactions (allergic reactions or symptoms) are an expected consequence of the therapeutic process of gradual desensitisation to the allergen. Appropriate information, in particular regarding the GI adverse reaction and systemic allergic reactions have been included in the sections 4.4 and 4.8 of the SmPC. The package leaflet has been updated accordingly. Anaphylaxis/ systemic allergic reactions is an important identified risks listed in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

In toddlers (1-3 years) a more favourable safety profile compared to older subjects (4-17 years) has been observed. As such, no severe systemic allergic reactions (anaphylaxis) were seen. Whereas, anaphylaxis was reported in children aged 4 to 17 years in 10 subjects (1.1% overall), over time. Eight of the 10 subjects who experienced anaphylaxis had potential cofactors. The management with co-factors requires high compliance, as outlines in the product information. Thus, this compliance and shared-decision process is in general high in parents of little children, but gets less in older children, adolescents or young adults. Therefore, the observation of less or less severe adverse events may (also) be associated with better a disease management in general. Still, although generally the safety profile represents as being less severe in the younger age group with n = 98 Palforzia treated children in ARC005, the occurrence of allergic reactions, including anaphylaxis, remains.

Next to severe allergic reactions, recurrent GI events such as abdominal pain, nausea and vomiting represent a concern in all age groups. As these hamper the daily and continuous treatment intake, GI events are the main reason for study discontinuation. Moreover, GI symptoms trigger concerns on a possible development of EoE in patients. Associations with IgE- or non-IgE-mediated GI diseases are not fully understood. Moreover, correspondent diagnosis is often difficult, especially in young infants. In this context, occurrence of the non-IgE mediated FPIES should be considered in any toddler with significant food associated GI symptoms. Currently, there is no sufficient data, showing that especially young infants with no known history of peanut ingestion might develop (atypical) FPIES triggered by peanut. However, according to literature, "*Peanut food protein-induced enterocolitis syndrome appears to be increasing, possibly related to early introduction. Increased awareness of this trend is crucial, particularly given the already high rate of misdiagnosed food protein-induced enterocolitis syndrome*"[1]. Although in the mentioned retrospective analysis, no cases of peanut FPIES with onset after age 12 month have presented at their institution, it should be noted that so far, the data is extremely thin[1]. Moreover, cases with FPIES are described which had positive specific IgE to the FPIES food (atypical FPIES)[2], and "*that specific IgE to the trigger was present in some cases throughout the course of the disease and disappeared or developed during the course in other children*"[3].

[1] Lopes JP, et. al Peanut-induced food protein-induced enterocolitis syndrome (FPIES) in infants with early peanut introduction. J Allergy Clin Immunol Pract. 2021 May;9(5):2117-2119
[2] Caubet et al. J Allergy Clin Immunol. 2014; 134: 382–389
[3] Gernert S, et al. Allergol Select. 2022 Oct 5;6:233-240

Consequently, as also mentioned the previous section, “A history of food protein-induced enterocolitis syndrome (FPIES)” and “A history of failure to thrive” were included as contraindication in the product information.

In general, it should be noted that the “comparison” of study safety data of one single study (in toddlers) with less than 100 exposed subjects at all, with a pooled safety data set like the integrated safety population with 944 subjects aged 4-17 of age, needs to be considered with caution. Safety and efficacy results might not only be influenced by the effect of the medicinal drug itself, but also by high compliance and anticipatory action, such as the proactive handling of co-factors by parents of young children compared to compliance of adolescents or young adults.

3.6. Effects Table

Table 32: Effects Table for Palforzia in the treatment of patients aged 1 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older (data cut-off: 22 July 2022).

Effect	Short Description	Unit	Treatment Palforzia (n=98)	Control Placebo (n= 48)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Desensitisation response rate	Proportion of subjects (1-3 years old) tolerating a single dose of at least 1000 mg at the exit of DBPCFC	%	68.4 (95% CI 58.2, 77.4)	4.2 (95% CI 0.5, 14.3)	Statistically significant and clinically meaningful	Study ARC005
Unfavourable Effects						
Vomiting	Incidence of vomiting	%	15.3	0	GI disorders were the most common reasons leading to discontinuation of treatment.	Study ARC005 (see also Table 20 in this report)
Abdominal pain	Incidence of abdominal pain	%	15.3	6.3		
Urticaria	Incidence of urticaria	%	30.6	29.2	Urticaria and cough were the most commonly reported symptoms of systemic allergic reactions.	
Cough	Incidence of cough	%	20.4	4.2		

Abbreviations: DBPCFC: double-blind placebo-controlled food challenge, GI: gastrointestinal, CI: confidential interval.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with Palforzia resulted in a statistically significant treatment effect over placebo in the proportion of toddlers aged 1 to 3 years who tolerated peanut protein with no more than mild

symptoms at the exit DBPCFC after (according to the study design) 6 months of maintenance treatment. This treatment effect was observed for the primary and key secondary endpoints of desensitisation response and maximum severity of symptoms, as well as in exploratory efficacy endpoints.

The use of Palforzia in toddlers aged 1 to 3 years raises no new safety concerns, with a safety profile that was similar or milder than that seen in older children aged 4 to 17 years. Altogether the safety population remains limited therefore the occurrence of more severe reactions and anaphylaxis cannot be excluded. Self-injectable adrenaline (epinephrine) must be available to the patient at all times. Occurrence of GI symptoms are of importance and should be closely monitored. Although not fully understood these may lead to the development of IgE- or non-IgE mediated GI diseases. Appropriate contra-indication, special warnings and precaution for use have been included in the product information to mitigate the occurrence of these risks.

3.7.2. Balance of benefits and risks

The benefit-risk balance of Palforzia for the treatment of toddlers with peanut allergy is considered positive. The beneficial effects have been shown in study ARC005, with results being in line with those received in former pivotal phase 3 studies ARC003 and ARC010. Palforzia showed meaningful improvements across all endpoints in toddlers.

Although the rate of TEAEs is high, most events were mild or moderate in intensity. The rate of SAEs was low and no new safety risks compared to the indication in patients 4-17 years of age were identified. Still, occurrence of GI symptoms and possible development of IgE- or non-IgE mediated gastrointestinal diseases should be monitored with caution.

3.8. Conclusions

The overall B/R of Palforzia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	None

Grouped variation consisting of:

C.I.6.a (Extension of indication): Extension of indication to include treatment of patients 1 to 3 years old for PALFORZIA, based on final results from study ARC005; this is a Phase 3 randomised, double-blind, placebo-controlled Peanut Oral Immunotherapy Study of Early Intervention for Desensitisation (POSEIDON) to evaluate the safety and efficacy of peanut powder in terms of superiority of placebo in children of 1 year to less than 4 years of age with peanut allergy. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The Package Leaflet and Labelling were updated accordingly. Version 1.2 of the RMP has also been updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to update the list of local representatives in the Package Leaflet. As part of the application the MAH is requesting a 1-year extension of the market protection.

B.II.e.5.a: Introduction of a new pack-size of 16 capsules of 1 mg (Level 0) in blisters for PALFORZIA, 1 mg, oral powder in capsules for opening.
Due to the lack of a suitable pack-size for the up-dosing phase for patients 1 to 3 years old, a new pack size Level 0 for the up-dosing phase will be introduced. Consequently modules 3.2.P.1 and 3.2.P.7 were updated. Labeling was updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update module 3.2.P.3.1 to take out the EU importation site (editorial change).

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0103/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Palforzia-H-C-004917-II-0014-G’.