NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Palforzia for treating peanut allergy [ID1282]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Palforzia for treating peanut allergy [ID1282]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from Aimmune Therapeutics UK Ltd
   a. Company submission
   b. Company submission addendum

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Allergy UK
   b. Anaphylaxis Campaign

4. **Evidence Review Group report** prepared by Aberdeen Health Technology Assessment Group

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**
   - Company response
   - Additional evidence supplement

7. **Technical engagement responses and statements from experts:**
   a. Dr Mich Lajeunesse - clinical expert, nominated by Aimmune Therapeutics
   b. Professor Adam Fox - clinical expert, nominated by Aimmune Therapeutics
   c. Sarah Baker and Hannah Bell - patient experts, nominated by Anaphylaxis Campaign

8. **Technical engagement responses from consultees and commentators:**
   a. Anaphylaxis Campaign
   b. British Society for Allergy and Clinical Immunology (BSACI)

9. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen Health Technology Assessment Group
   - ERG critique
   - ERG Addendum

Any information supplied to NICE which has been marked as confidential, has been

redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palforzia for treating peanut allergy

[ID 1282]

Document B

Company evidence submission

May 2021

File name	Version	Contains confidential information	Date
ID1282_Palforzia_Document_B_ ACIC_FINAL	**3.0**	**Yes**	**May 2021**

Contents

Tables and figures

Abbreviations

AAI	Adrenaline auto-injector
A&E	Accident & emergency
AE	Adverse event
ANCOVA	Analysis of covariance
APC	Antigen-presenting cell
APPEAL	Allergy to Peanuts ImPacting Emotions And Life
BIW	Twice weekly
BNF	British National Formulary
BMI	Body mass index
BSACI	British Society for Allergy and Clinical Immunology
CC	Complications
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBPCFC	Double-blind placebo-controlled food challenge
EACCI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
EoE	Eosinophilic oesophagitis
EPAR	European public assessment report
EPIT	Epicutaneous immunotherapy
EQ-5D	EuroQol-five dimension
EQ-5D-Y	EuroQol-five dimension-Youth
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy-Related Quality of Life Questionnaire
FcR	Fc receptor
FDA	US Food and Drug Administration
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HADS	Hospital Anxiety and Depression Scale
HDA	High-dose antihistamine
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICER-US	Institute for Clinical and Economic Review in the US market
IDE	Initial dose escalation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
ITT	Intention-to-treat
LS	Least squares
LT	Leukotriene
LY	Life-year
LYG	Life-year gained
MCID	Minimal clinically important difference
MED	Minimal eliciting dose

MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
MTD	Maximum tolerated dose
N/A	Not applicable
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service
NMB	Net monetary benefit
NICE	National Institute for Health and Care Excellence
OIT	Oral immunotherapy
OD	Once daily
OWSA	One-way sensitivity analysis
PA	Peanut allergy
PAPRIQUA	Peanut Allergy impact on PRoductivity and QUAlity of life
PG	Prostaglandin
PIP	Paediatric investigational plan
PLD	Patient-level data
PPPY	Per person per year
PSA	Probabilistic sensitivity analysis
psIgE	Serum peanut-specific immunoglobulin E
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q	Quartile
QALY	Quality-adjusted life-year
QOD	Every other day
QW	Once weekly
RCPHP	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SHELF	Sheffield Elicitation Framework
SLIT	Sublingual immunotherapy
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SPT	Skin prick test
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TH2	Helper T-cell 2
TSQM-9	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
US	United States

B.1 Decision problem, description of the technology and clinical care pathway

- Peanut allergy is one of the most common food allergies, affecting between 0.5% and 2% of children in the UK. In the majority of cases (80%), peanut allergy persists into adulthood.
- Anaphylaxis or severe anaphylactic reactions are unpredictable and the most severe manifestation of an allergic reaction to peanuts. Anaphylaxis is systemic and can be fatal, with peanut causing 16% of all cases of fatal food-induced anaphylaxis in children.
- Allergic reactions are unpredictable. It is not possible to predict when a reaction will next occur or the severity of subsequent reactions. This leads to substantial stress and anxiety for children with peanut allergy and their caregivers which is comparable to other paediatric chronic illness populations, such as type 1 diabetes.
- Diagnosis of peanut allergy is usually based on clinical history, followed by skin prick test and/or serum specific IgE test to prove allergen sensitisation.
- Current peanut allergy management relies on peanut avoidance and emergency medication when an allergic reaction occurs. Besides Palforzia, there are no licensed treatments for peanut allergy and consequently there is a significant unmet need for both children and caregivers alike.
- Peanut avoidance is extremely challenging for children and caregivers to achieve in practice as peanut is found in trace amounts in many foods making food warning labels difficult to interpret. Children and their caregivers must also be competent and confident in administering emergency adrenaline auto-injection when systemic allergic reactions occur. This is another source of fear and anxiety making the daily process of managing peanut allergy extremely stressful and challenging.
- The fear of unpredictable and life-threatening allergic reactions, and the burden of peanut avoidance in terms of limitations on daily activities and social isolation have a significant impact on children's and caregivers' quality of life.
- Peanut allergy also incurs significant direct medical and societal costs due to productivity losses and increased out of pocket expenses for caregivers.
- Palforzia is the first licensed treatment for children aged 4 to 17 years with a confirmed diagnosis of peanut allergy. A positive recommendation from NICE for Palforzia would provide children with peanut allergy, their caregivers and clinicians with the first treatment option for peanut allergy.

B.1.1 Decision problem

The submission covers the full marketing authorisation for Palforzia (peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts)) for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. The decision problem addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Children with peanut allergy aged 4 to 17 years and adults who started treatment as a child.	Patients aged 4 to 17 with a confirmed diagnosis of peanut allergy who are under the care of a specialist physician, including patients who turn 18 years old during therapy	To be in line with the final licensed indication for Palforzia (peanut protein as defatted powder of *Arachis hypogaea L*., semen (peanuts))
Intervention	AR101	Palforzia (peanut protein as defatted powder of *Arachis hypogaea L*., semen (peanuts))	Palforzia is the brand name for AR101
Comparator(s)	Established clinical management without Palforzia including allergen avoidance, symptomatic treatments such as antihistamines and emergency medication	As per the scope	N/A
Outcomes	The outcome measures to be considered include: • peanut allergy desensitisation • systemic allergic reactions (including anaphylaxis) • frequency and severity of symptoms after accidental exposure to peanut • discontinuation of treatment • adverse effects of treatment • health-related quality of life.	As per the scope. It should be noted that: • Peanut allergy desensitisation, was evaluated in the clinical trials by challenge doses of <300 mg, 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively), 1000 mg (2043 mg cumulatively) and 2000 mg (4043 mg cumulatively) peanut protein in a double-blind placebo-controlled food challenge (DBPCFC). • Allergic reactions (including anaphylaxis) and symptoms are considered separately due to treatment (safety outcome) versus due to accidental exposures to peanut (efficacy outcome). Accidental exposures to peanut requiring treatment are presented with and without the requirement of adrenaline, in line with clinical trial definitions. • As accidental exposures to peanut were relatively uncommon in the trials, data on the maximum severity of symptoms during the DBPCFC are additionally presented as a	

		surrogate for severity of symptoms after a real-world accidental exposure to peanut. • Health-related quality of life (HRQoL) impacts are considered both for patients and their caregivers.	

DBPCFC: double-blind placebo-controlled food challenge; N/A: not applicable; HRQoL: health-related quality of life

B.1.2 Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

The UK summary of product characteristics (SmPC) and the EPAR report are included in Appendix C. The technology being appraised is described in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	*Palforzia (peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts))*
Mechanism of action	*The precise mechanism of desensitisation provided by defatted powder of Arachis hypogaea L., semen (peanuts) is not currently fully understood, but the current evidence of the human immune response to oral immunotherapy (OIT) is summarised in this dossier. Palforzia is a complex biologic drug used with a structured dosing approach that builds on a century of OIT research. With OIT, the specific allergenic proteins are ingested initially in very small quantities, followed by incrementally increasing amounts that can result in the ability to mitigate allergic reactions to the allergen over time (see Palforzia treatment* overview In contrast to current management, Palforzia is an etiological treatment, addressing the underlying mechanism of peanut allergy disease, and ultimately modifying the patient's immunologic response to peanut (see Figure 1). Figure 1*).*
Marketing authorisation status	*Approved* *Centralised procedure Dec 21, 2020*
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	*Palforzia is indicated for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.* *Palforzia may be continued in patients 18 years of age and older.* *Palforzia should be used in conjunction with a peanut-avoidant diet.*

Method of administration and dosage

Palforzia should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases.
Initial dose escalation and the first dose of each new up-dosing level are to be administered in a health care setting prepared to manage potential severe allergic reactions.
Self-injectable adrenaline (epinephrine) must be available to the patient at all times.

Dosage: administered in 3 sequential phases: Initial dose escalation, up-dosing, and maintenance. For each dose level during up-dosing, the doses given in clinic and at home should be from the same batch to avoid variations in the potency range
Initial dose escalation is administered in sequential order on a single day beginning at 0.5 mg and completing with 6 mg.

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

Up-dosing: Initial dose escalation must be completed before starting up-dosing. Up-dosing consists of 11 dose levels and is initiated at a 3 mg dose

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

Maintenance therapy: All dose levels of up-dosing must be completed before starting maintenance. The maintenance dose of Palforzia is 300 mg daily.

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

Daily maintenance is required to maintain the tolerability and clinical effects of Palforzia. Efficacy data currently are available for up to 24 months of treatment with Palforzia. No recommendation can be made about the duration of treatment beyond 24 months. The effect of stopping treatment on maintenance of clinical efficacy has not been evaluated.

Additional tests or investigations

No companion diagnostic tests

List price and average cost of a course of treatment

[redacted]
(NB These prices are still to be agreed with the Department of Health)

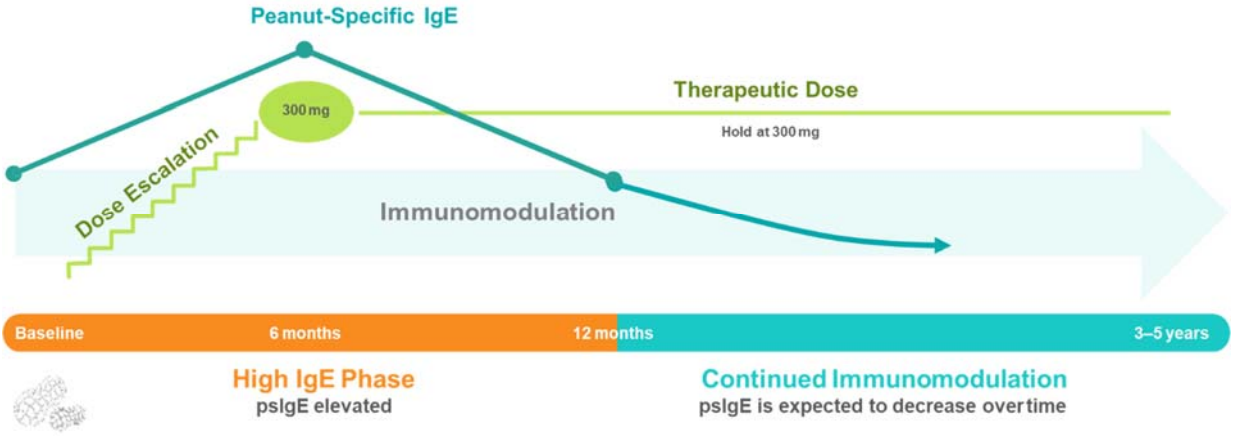
Patient access scheme (if applicable)	N/A

Source: Annex I SmPC[1]

Palforzia treatment overview

In contrast to current management, Palforzia is an etiological treatment, addressing the underlying mechanism of peanut allergy disease, and ultimately modifying the patient's immunologic response to peanut (see Figure 1).

Figure 1: Biological mechanism of oral immunotherapy



IgE: immunoglobulin E; ps: peanut-specific

Palforzia has been developed as an oral immunotherapy (OIT) to help protect patients with peanut allergy from systemic allergic reactions, including anaphylaxis.

With Palforzia, patients ingest controlled, increasing amounts of medicine over time on a daily basis until a target dose is reached, which trains their immune system to tolerate significantly higher amounts of peanut protein than they are allergic to, resulting in reduced frequency and severity of allergic reactions.

Palforzia contains an array of characterised peanut allergens. These peanut allergens consist of a natural mixture of proteins from Ara h 1 through to Ara h 17,[2] with sensitisation patterns to peanut allergens being dependent on geographical location.[3] For instance, key peanut allergens that trigger allergic reactions in the USA include Ara h 1, Ara h 2, and Ara h 3[3] whereas in European countries, Ara h 2 is the main allergen responsible for eliciting systemic reactions.[4] Palforzia combines a highly characterised agent with a consistent and reliable profile of allergenic proteins that includes all relevant allergens.

B.1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

Disease definition and epidemiology

Food allergy is defined as an immune-mediated hypersensitivity reaction to the ingestion, inhalation or skin contact of food and may be divided into Immunoglobulin E (IgE) mediated (immediate-onset) reactions and non IgE-mediated (delayed-onset) reactions.[5] Peanut allergy is one of the most common food allergies, affecting between 0.5% and 2% of children in the UK.[6] Although fatalities are relatively rare, peanut allergy accounts for 16% of all cases of fatal food-induced anaphylaxis (severe anaphylactic reaction) in children and 22% in adults in the UK.[7] Data from the European Anaphylaxis Registry show that among children and adolescents (<18 years), 27.2% of anaphylactic reactions related to food were triggered by peanuts.[8]

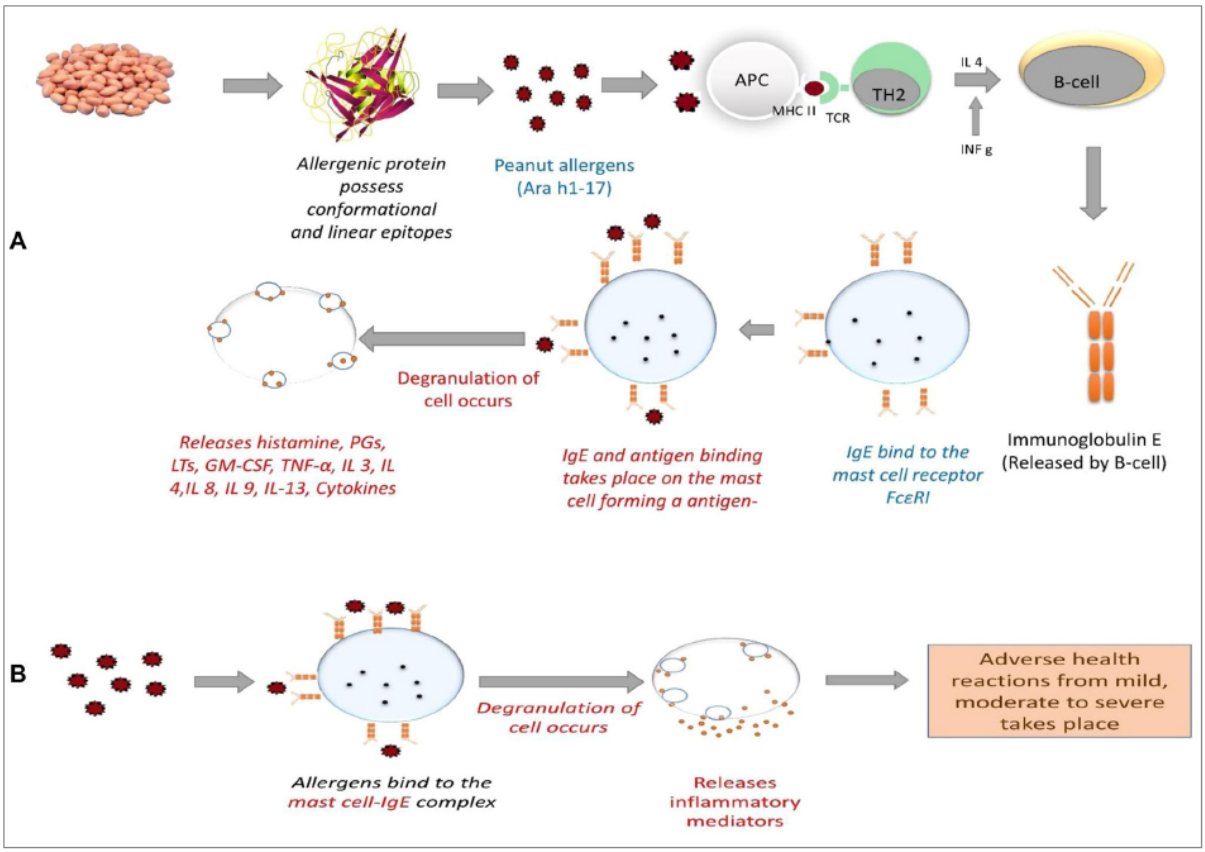
The prevalence of peanut allergy has increased significantly in recent decades.[9] In the UK, 635 per 100,000 children under 18 years of age suffered from peanut allergy in 2015, versus 116 per 100,000 in 2000 (5-fold increase).[9] However, whilst prevalence estimates are available, there are challenges in robustly defining the number of patients with peanut allergy primarily due to variability in diagnostic criteria and definitions and to diagnostic methods deployed by physicians.

Pathophysiology and risk factors for peanut allergy

Peanuts (*Arachis hypogaea*) contain 17 allergens, Ara h 1 to Ara h 17, with different degrees of allergenicity.[10] Over 50% of peanut-allergic sufferers have antibodies to Ara h 1, 2, 3 and 6.[11] In individuals who are susceptible to peanuts, the allergenic proteins produce a type I hypersensitive immune reaction mediated by the immunoglobulin E (IgE) pathway.[12-14] This results in the release of inflammatory mediators including, among others, histamine, prostaglandins, leukotrienes and cytokines (see Figure 2).[12] In addition, the cells also produce interleukins (IL-4 and 13) and other cytokines and chemokines, which trigger a late-phase reaction by which eosinophils, lymphocytes and monocytes are recruited to release additional

inflammatory mediators and cytokines. It is the combined action of these inflammatory mediators that leads to the reaction to peanuts.

Figure 2: Mechanism of peanut allergy sensitisation upon exposure to peanut protein allergen (A: initial exposure; B: re-exposure)



APC: antigen presenting cell; FcR: Fc receptor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IgE: immunoglobulin E; IL: interleukin; LT: leukotriene; MHC: major histocompatibility complex; PG: prostaglandin; TCR: T-cell receptor; TH2: Helper T-cell 2; TNF: tumour necrosis factor
Source: Shah et al. 2019.[12]

Risk factors

A number of genetic and environmental risk factors can predispose individuals to peanut sensitivity, including allergic immune comorbidities, exposure to microbes, allergen avoidance and nutritional factors.[10,14,15] The Learning Early about Peanut Allergy (LEAP) screening study showed that egg allergy and severe atopic dermatitis are associated with increased risk of peanut allergy in infancy.[16] In addition, milk allergy, lack of breastfeeding, younger age and higher Ara h 2 and peanut-specific IgE levels are risk factors for peanut allergy. Exposing high-risk children to peanuts at an early age can decrease the risk of developing allergy.[15,16]

Severity of reactions

The frequency and severity of allergic reactions are highly unpredictable, and the severity of symptoms experienced during an exposure to peanut may not be consistent with the severity of future reactions.[17] The severity of an allergic reaction can be influenced by a number of factors, including a history of anaphylactic reaction to peanut, comorbidities, medical events and other cofactors that may decrease the allergic reaction threshold following exposure (e.g., stress, fatigue, sleep deprivation, menstruation, etc.).[17-20] In addition, risk-taking behaviour among adolescents and young adults, such as failure to avoid triggers, failure to carry an adrenaline auto-injector (AAI), and alcohol or drug use, are also thought to contribute to severe or fatal anaphylaxis.[7,21] Overall, it is not possible to predict the likelihood or severity of an individual's allergic reaction in response to accidental exposure to peanut, even with detailed knowledge about a patient's previous reactions.[17]

Natural history and clinical presentation

Most individuals with peanut hypersensitivity will initially present to their general practitioner (GP) or accident & emergency (A&E) department having had an allergic reaction caused by peanut exposure.[17] In general, symptoms affect the skin, gastrointestinal tract, respiratory and cardiovascular systems. Most common symptoms include rash, vomiting, abdominal pain, wheezing and throat tightness.[10,17,22-24] Anaphylaxis or severe anaphylactic reaction is the most severe manifestation of an allergic reaction to peanuts; it is systemic and can be fatal.[10,17,22-24] Patients who have a severe anaphylactic reaction can have life-threatening airway and/or circulation problems usually associated with skin and mucosal changes.[17,25] Typically, respiratory arrest occurs after 30–35 minutes of exposure.[17,25,26] As stated earlier, the severity of a reaction does not predict the likelihood or severity of future reactions.[17]

In real life, the median estimated amount of peanut triggering an allergic reaction is 125 mg of peanut protein,[27] (approximately half of a peanut kernel[28]) although an allergic reaction can be elicited by exposure to trace amounts (less than 5 mg) of peanut protein, making the review of peanut allergy labelling difficult.[27,29] More than 95% of reactions occur within 20 minutes, with some occurring within seconds and

others occurring up to 2 hours after contact.[10,23] In addition, 20% to 30% of sufferers can experience a late-phase reaction in which symptoms recur 1 to 8 hours after the initial symptoms resolve.[10]

Peanut allergy resolution

Unlike allergies to milk, egg and soy which can resolve in 60% of children within the first 6 years of life due to natural tolerance, 80% of childhood-onset peanut allergy persists into adulthood.[30-32] In the remaining 20% of cases, who cannot be identified in advance, resolution often occurs between the ages of 4 and 6 years.[30,33]

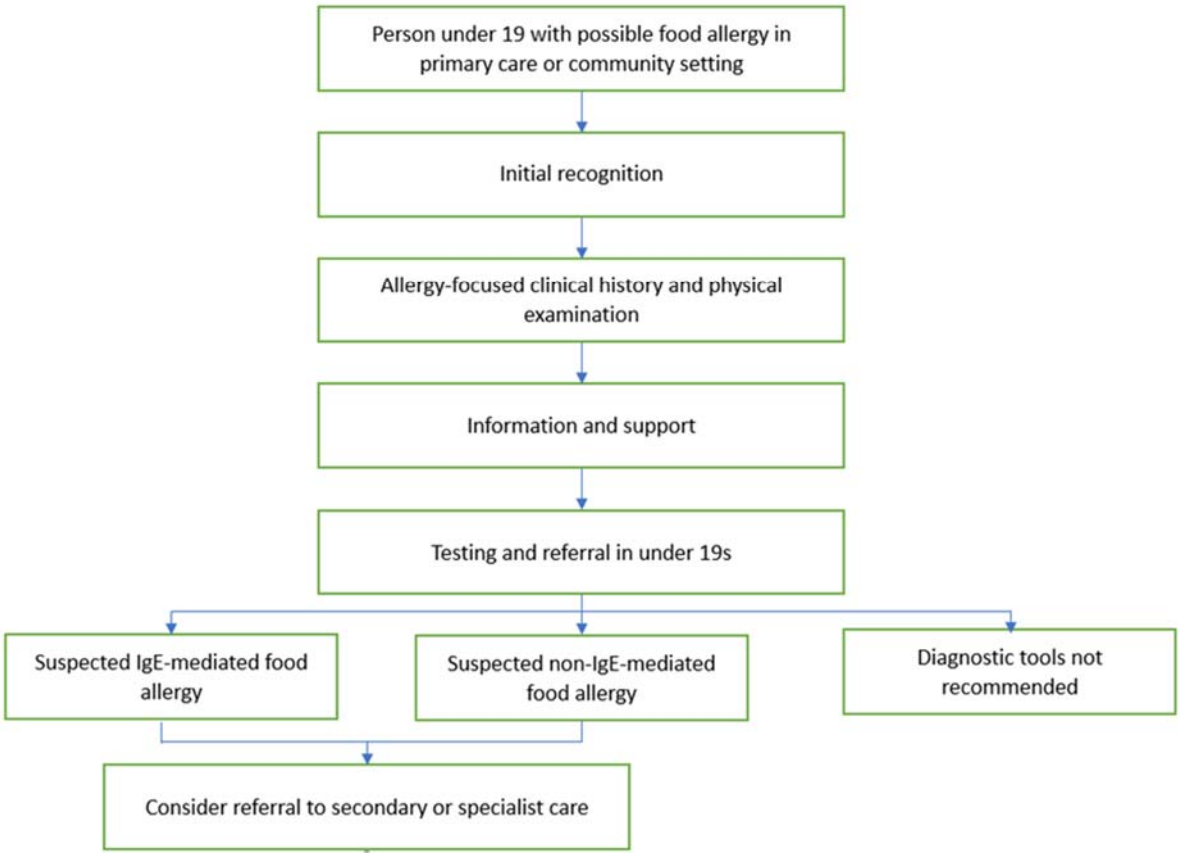
Comorbidities

A number of comorbidities are common among children with peanut allergies[27,34-36] and this is reflected accordingly in clinical trials.[37,38] For example, in the PALISADE randomised controlled trial (RCT),[39] more than half of participants with peanut allergy reported having a comorbid condition including allergic rhinitis ([redacted]), atopic dermatitis ([redacted]), asthma ([redacted]), and multiple food allergies ([redacted]) such as allergies to cashew, hazelnut or hen's egg.

1.3.2 Treatment pathways

In the UK, clinical guidelines for the diagnosis and treatment of food allergy are available from the Royal College of Paediatrics and Child Health (RCPCH)[5] and, specifically related to specialist care, from the British Society for Allergy and Clinical Immunology (BSACI).[14] The National Institute for Health and Care Excellence (NICE) guideline and pathway for treating and referring for food allergy in under 19 years of age suggests diagnosis is made at a primary care level (see Figure 3).[40] However (and based on clinical feedback) in clinical practice, GPs tend to refer patients to secondary or specialist care for formal diagnosis and treatment.

Figure 3: NICE Pathway for the diagnosis and management of food allergy



IgE: immunoglobulin E
Source: NICE Pathway, 2020[40]

Diagnosis

In the UK according to the RCPCH, clinical history is paramount for the diagnosis of food allergy.[2] Currently, formal diagnosis tends to be made on referral to secondary or specialist care. Clinical history is tailored to the presenting symptoms and age of the patient, and includes assessment of presenting symptoms, personal and family history, dietary history and important comorbidities.[14,22] Based on the results of allergy focused clinical history, investigations tailored to the suspected underlying mechanism are conducted. Appropriate investigations for suspected IgE mediated immediate/acute reactions include skin prick and serum specific IgE testing to prove allergen sensitisation.

Oral Food Challenge

For unclear clinical history or sensitisation results, medically supervised oral challenge at secondary or specialist care level may be conducted in a safe and controlled

environment where facilities for paediatric resuscitation and advanced life support exist.

During the oral food challenge, increasing measured doses of a test allergen are administered sequentially until symptoms occur that prevent further dose increases. This allows the assessment of the highest tolerated dose of an allergen and the associated dose-limiting symptoms.

The NICE guideline 'Food Allergy in under 19s: assessment and diagnosis' (2011) notes that food challenges are cumbersome and time-consuming and that there are some safety risks involved. Oral food challenge is therefore advised not to be performed in primary care or community settings.[22] As captured in a recent survey of 109 allergists,[41] oral food challenge was only rarely used in the UK to confirm the initial diagnosis of peanut allergy (3% of 35 UK allergists surveyed versus 66% and 49% performing skin prick and IgE tests, respectively).

The double-blind, placebo-controlled food challenge (DBPCFC), although being the gold standard for food allergy diagnosis, is mostly reserved for research purposes. It is considered by regulators as a valid and robust surrogate for accidental food exposures in real life. Further explanations of this important tool are included in Section B.2.3.1.

Current management

Currently, the standard of care for management of peanut allergy is limited to strict avoidance, treatment of allergic reactions in the case of exposure to peanut (symptomatic treatment), and patient and caregiver education to understand and manage symptoms, should an exposure occur.[14] Depending on the severity of the reaction post-exposure, rapid administration of rescue medications, such as intramuscular adrenaline (AAIs), is recommended.[42] Consistent with these recommendations, in a recent study 77% of allergists in the UK (n=35) reported discussing the usage of AAI and 86% discussed allergen avoidance with caregivers of children with a potential peanut allergy diagnosis during initial consultation.[41]

Anaphylactic reactions require complicated management, which comprises early self-administration of AAI by patients and caregivers, who need to be regularly trained on

recognising the signs and symptoms of systemic allergic reaction and be competent and comfortable with using AAI. Emergency management by healthcare practitioners includes supportive care for the patient's breathing, airway and circulation, along with an observation period and early recognition of potential rebound reactions. Despite the availability of clinical guidelines, there remains confusion about the indications, dose and route of administration of adrenaline by healthcare practitioners.[25]

Avoidance is the cornerstone of the management strategy for peanut allergy sufferers and involves a comprehensive oversight plan that includes advice on how to avoid peanuts and peanut products.

In order to have a pre-emptive or reactionary management plan that is truly effective, it cannot be localised solely to the child with peanut allergy and it has to extend to his or her entire extended social network, which can include parents, grandparents, teachers and friends.[14] The unpredictability of allergic reactions and the potential to have an anaphylactic reaction means that children need to carry two AAIs at all times, and there exists a concomitant reliance on school, care providers and healthcare professionals to be able to deal with severe reactions. Therefore, it is critical to educate patients and their families and caregivers on food allergen avoidance. Even with increased awareness and education on avoidance, unintended exposure remains a major concern. For example, a recent large study in a Canadian cohort demonstrated that accidental exposures continue to occur despite increased awareness.[43] The annual incidence reported in this study was 12.4%, with 377 of the 567 (66.5%) accidental exposures resulting in a moderate or severe reaction.[43] Similarly, in a recent study conducted in the Netherlands, despite counselling and education, 46% of food allergic patients reported an allergic reaction after unintended exposure, and of these, 55% were patients with peanut allergy.[44]

1.3.3 Quality of life and economic burden of peanut allergy

Quality of life

The constant stress of peanut avoidance and anxiety about potential life-threatening reactions can have a significant negative impact on quality of life (QoL) for both children and their families/caregivers, and can also significantly restrict their daily activities.[45-47]

Children

Children with peanut allergy report high levels of psychological stress, including anxiety, worry and/or fear related to experiencing an allergic reaction or anticipating the risk of one.[47,48] Children with peanut allergy reported having lower QoL, greater fear of adverse events and more anxiety about eating than children with insulin-dependent diabetes mellitus (N=40).[47] The constant vigilance to avoid peanut exposure is a source of stress and anxiety, negatively affecting daily and social activities,[48,49] such as eating at home or in restaurants, travelling, attending birthday parties and using public transportation.[46-48] Precautionary food product labelling of commercial food products, such as “may contain” or “in a facility with”, can be misinterpreted, making avoidance more difficult and further contributing to the distrust of food. Patients also fear having a reaction surrounded by unknown people or in a situation where they are unable to gain immediate help. As a consequence, individuals with peanut allergy tend to avoid social events to avoid exposure to peanut and this contributes to feelings of isolation that impact well-being and is particularly stressful among adolescents.[50] Overall, children with peanut allergy feel more threatened by potential hazards and more restricted in their daily activities away from home compared to children with diabetes.[47] Having to carry an AAI and use it in an emergency situation under great physical and emotional stress is another source of fear and anxiety.

Due to these factors, there is a significant disutility associated with peanut allergy and food allergy in general among children. Based on two Danish cohorts of individuals with clinically confirmed peanut allergy, a recent study estimated a lifetime Disability Adjusted Life Year (DALY) impact of 3.4 DALYs due to peanut allergy.[51] Similarly, a case control study conducted in the Netherlands and the UK found the utility decrement associated with having food allergy to be 0.08,[52] whilst another case control study in Sweden found this decrement to be 0.10.[53] In the UK more specifically, the Peanut Allergy impact on PRoductivity and QUAlity of life (PAPRIQUA) study was a cross-sectional survey to assess caregiver-reported impact of living with peanut allergy on children’s QoL.[54] Results demonstrated that caregiver-reported QoL of children and adolescents with peanut allergy was lower than that of the general UK young adult population, and that the effect of peanut allergy on QoL was significantly associated with caregiver perceived severity of their child’s allergy ($p<0.05$).[54] The

mean health utility for the children and adolescents in the study as a whole, as assessed by the EuroQol five-dimension-Youth (EQ-5D-Y) measure, was 0.873 (standard deviation [SD] 0.231), although those with perceived severe peanut allergy reported lower utility (0.768; SD 0.292). No population norms are available for the EQ-5D-Y; however, the population norm for young adults (aged 18-24 years, using EQ-5D-3L) is 0.940,[55] indicating a potentially very significant disutility due to peanut allergy.

Children surveyed as part of the Allergy to Peanuts ImPacting Emotions And Life (APPEAL-2[48]) study reported significant emotional impact and disruption to their daily lives (see quotes in Figure 4).

Figure 4: Illustrative comments from APPEAL-2 child participants

- "I feel really stressed out sometimes, I feel annoyed about it. I feel... sometimes depressed, like... why me?" *[Child, Age 11, UK]*
- "There always is danger around me. For a normal person, (…) they don't have that danger*." [Adolescent, Italy]*
- "…if I have any doubt, I prefer to stay hungry." *[Adolescent, Spain]*
- "So I tell [my friends] but it's useless because they don't understand. They only understand that they should stay away from me." *[Child, France]*
- "I never go (to a restaurant) because when we ask them peanut-free dishes, they're not even sure of what dishes do and don't have peanuts in it. (…) I eat at home." *[Adolescent, France]*
- "[Friends without PA] are on a higher level independent from their parents. I need the support from my mother." *[Adolescent, Denmark]*

Families and Caregivers

Peanut allergy also places a significant burden on families. Caregivers and parents of children with food or peanut allergies can suffer from significantly greater anxiety (average score [SD]: 39.04 [12.04] mothers of children with peanut allergy versus 32.8 [8.3] norm data for healthy adults; $p<0.05$) and stress (perceived stress average score [SD]: 25.13 [6.67] versus 19.62 [7.49] norm data; $p<0.05$) compared to the general population,[56] and lower well-being compared to parents in households without a child with a peanut allergy (average well-being score [SD]: 6.8 [0.29] versus 7.6 [0.37] controls; $p<0.10$).[52] The PAPRIQUA study examined the impact of peanut allergy on caregivers, and found that the mean anxiety levels of the overall sample of participants as assessed by the Hospital Anxiety and Depression Scale (HADS) were above the normal range (mean score for overall sample: 8.09, versus 0–7 for normal range; $p<0.001$).[57] The mean scores were also significantly higher than the population norm

for males, females, and for those who rated their child's peanut allergy as moderate or severe. Similarly, caregiver rates of probable clinical anxiety (moderate/severe HADS scores of >10) were approximately double the UK population norms (UK norms: mean 15.75%, males 12.5%, females 19%) and significantly higher for the total sample (31%; SD for the mean [z-score]: 4.2, p<0.001), males (26%, z: 2.9, p<0.01), females (35%, z: 2.9, p<0.001), and those reporting a child with moderate peanut allergy (33%, z: 3.9, p<0.001) or severe peanut allergy (33%, z: 2.2, p<0.05).[57]

Consequently, parents and caregivers surveyed as part of the APPEAL-2 study reported significant emotional impact and disruption to daily life and careers (see quotes in Figure 5).

Figure 5: Illustrative comments from APPEAL-2 carer participants

- "There's this whole plethora of stuff going round [Child] that has to be managed, that either me or [Partner] have to attend, to try and maintain some kind of status quo. So, I was a Deputy in [School]. So, it was a conversation where something has to give, and it felt like the right thing for it to be me. So, now I'm a part-time teacher" *[Carer, UK]*
- "So, I feel almost like we've had to educate family, especially my mum and dad, and it's like, 'Oh, he's allergic to peanuts.' 'Yes, and it can kill him,' do you know what I mean? And I feel like I have to follow that up with that. This allergy could kill him, and I always feel that I have to stress that. Going round to friends' houses and things like that." *[Carer, UK]*
- "I would say that it's the feeling of being constantly afraid that something happens….it's always there" [*Carer, Denmark]*"Social occasions are stress. [Child] going to anybody's house. I – not discourage – I'm mindful, I would say. I would, not shy away from, that's the wrong expression, I would be reluctant to push him really. I'm happier for him to be at home, so it's something that I don't have to think about." *[Carer, UK]*
- "I have to be permanently alert when it comes to eat something. And it is every day, several meals a day, social relationships, at school, at birthday parties, at home" [*Carer, Spain]*
- And now he's 11, a lot more independent, I'm starting to feel anxious about what this next bit's going to bring, because I'm not always there, hovering over him, checking things for him, so they are the biggest issues, more the worrying and the making sure people know" *[Carer, UK]*

Economic burden

In the UK, a retrospective matched-cohort study using national databases (the Clinical Practice Research Datalink [CPRD] and Hospital Episode Statistics [HES]) reported that the annual healthcare costs associated with peanut allergy were between £253 and £333 per person in 2015 compared to the general UK population.[9] This translates to excess costs of £33–44 million.[9] Annual excess costs were significantly higher for those with prior anaphylaxis (£662). These higher costs reflect the increased need among individuals with peanut allergy for primary care, hospital care and prescription medications (Table 3). Compared to individuals without peanut allergy, allergic

individuals had higher rates of primary care contacts, inpatient admissions, prescriptions, outpatient admissions, and A&E admissions, resulting in twice as many healthcare contacts overall.[9]

Table 3: Healthcare resource utilisation of individuals with peanut allergy versus peanut allergy-free individuals, matched by key demographic criteria and atopic status

	Peanut allergy cohort (N=9,320)	Peanut allergy-free, atopy matched* cohort (N=9,320)
Primary care contacts, PPPY	6.91	5.19
Inpatient admissions, PPPY	0.20	0.14
Prescription rate, PPPY	11.19	6.12
Outpatient admissions, PPPY	1.50	1.00
Accident & emergency admissions, PPPY	0.40	0.30
Total contacts, PPPY	20.20	12.80

*The peanut allergic cohort was matched to a peanut allergy free cohort based on age, GP practice, gender, registration year, and also on presence/absence of common atopic comorbidities, in order to adjust for associated resource use and costs of these conditions.
GP: general practitioner; PPPY: per person per year
Source: Scott 2019[9]

Peanut allergy is also associated with substantial indirect costs, as caregivers of children with peanut allergy report that it significantly impacts their careers. In a US survey of 1643 caregivers of children with food allergy, 71% of the overall economic cost of food allergy per child were opportunity costs of caregiver career activities forgone as a result of their child's allergy;[58] 25% of the overall cost were out of pocket costs of treatment and lost productivity. In a survey of UK parents of a child aged 4 to 15 years with peanut allergy, currently employed caregivers reported a mean of 1.6 absentee days and a mean of 1.9 days of impacted productivity in the past year as a result of their child's allergy.[57]

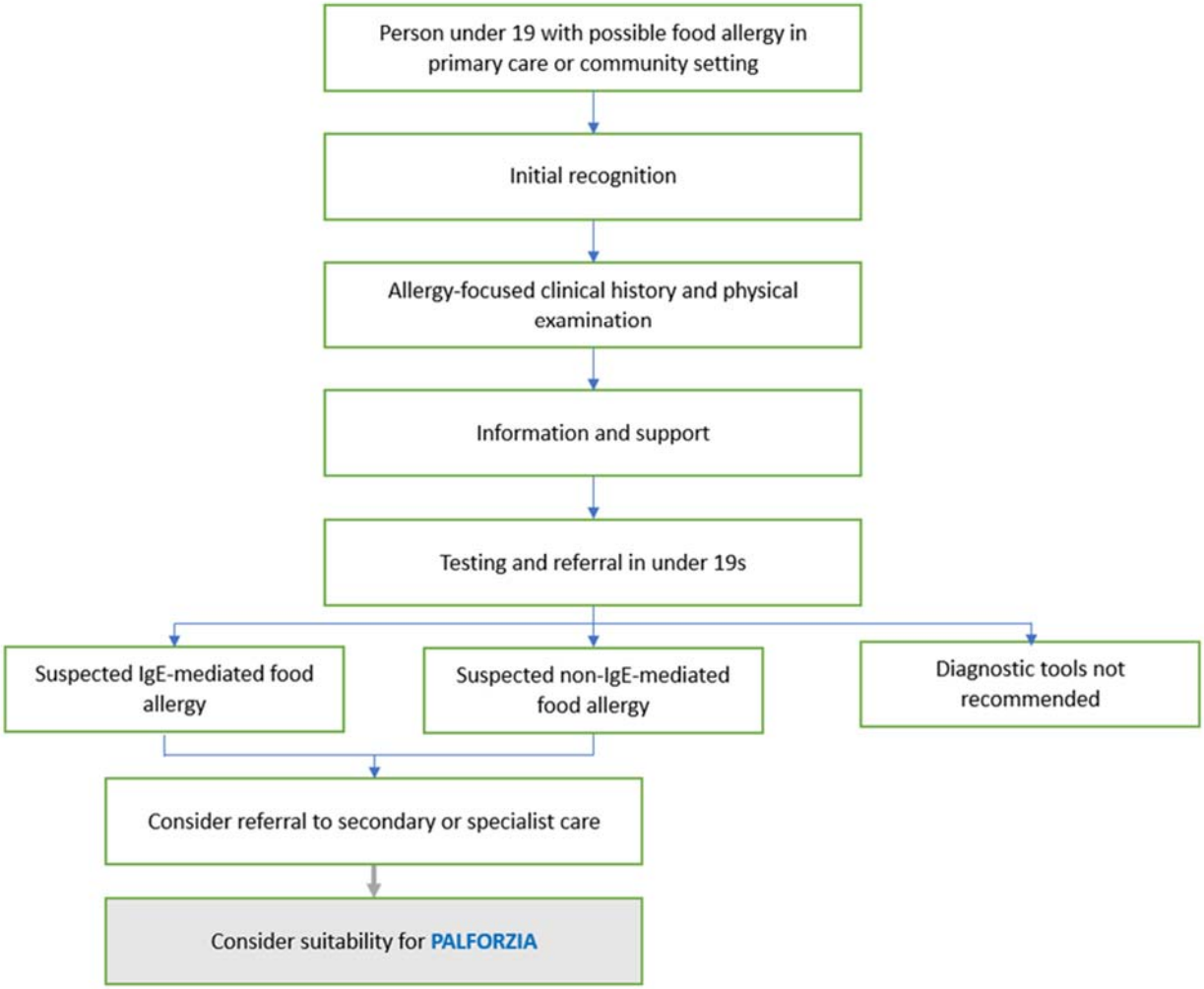
Peanut allergy also places an economic burden on schools. In the UK, schools are responsible for making arrangements to support pupils with medical conditions, including food allergy. Recommendations include ensuring that allergen labelling be available for any food provided by the school and educating staff and pupils on allergen avoidance and recognising food allergy reactions, among others. Further, school staff should be educated and trained in the administration of AAIs[14] which need to be kept up to date and stored in an accessible manner, meaning that school employees also have to take on a degree of the stress and QoL burden associated with a child's peanut allergy.

1.3.4 Place of Palforzia in the treatment pathway

Palforzia is the first licensed medicinal treatment for patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older. Palforzia should be used in conjunction with a peanut-avoidant diet. Furthermore, Palforzia should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases.

As per Figure 6, it is anticipated that Palforzia will be offered to suitable patients following diagnosis and referral to a paediatric allergy specialist in a secondary or tertiary care setting. [27]

Figure 6: Proposed pathway of care of peanut allergy with Palforzia (within the NICE pathway)



Unmet need

Palforzia, as the first licensed immunotherapy, represents a potential step change in the management of peanut allergy. There are currently no other licensed therapies for peanut allergy in Europe, avoidance alone is not a treatment strategy and there remains a significant unmet need.

While dietary avoidance may appear simple and manageable in theory, it is difficult to achieve in practice, which provokes allergic reactions requiring emergency treatment. Peanuts and peanut traces are found in many foods (e.g., cereals, ice cream, pre-packaged snack foods), making strict adherence to an avoidance diet difficult for children and families. Furthermore, avoidance is complicated by difficulty in interpreting food labels,[59,60] the presence of undeclared or inadvertent introduction of allergens in commercially prepared foods,[61,62] and inattention to or mistrust of food warning labels.[63] Additionally, foods prepared outside the home (e.g., at school, nurseries, restaurants, homes of family/friends) also present potential sources of exposure. Studies in the U.S., Canada and Europe attest to the ineffectiveness of vigilance alone to fully mitigate against the risks of peanut allergy. Accidental exposure to peanut can still occur, resulting in moderate or severe reactions in many cases (66.5%).[43]

Even if a peanut-product avoidance programme is successfully communicated and implemented and a plan is put in place to handle allergic reactions that arise in the event that avoidance fails, just the presence of these strategies themselves can cause unintended stress to the very people that they are designed to protect, and their caregivers.

Overall, despite the presence of prophylactic plans and intervention strategies post-peanut exposure, none of these options treat the disease itself and are themselves associated with significant burden to patients and families, given the lengths they have to go to in adjusting their daily lives to strictly avoid peanuts and maintain a significant and unavoidable risk of accidental exposures which may lead to reactions. Clearly, there is a significant unmet need for treatments such as Palforzia, which have the potential to improve the lives of children with peanut allergy by reducing the risk of severe allergic reactions. A positive recommendation for Palforzia would provide

children with peanut allergy, their caregivers, and clinicians access to the first treatment option for peanut allergy.

B.1.4 Equality considerations

Palforzia for the treatment of peanut allergy is not expected to cause any equity issues.

B.2 Clinical effectiveness

- Palforzia is the first licensed medicinal product for peanut allergy. It is an OIT specifically designed to reduce the frequency and severity of allergic reactions due to accidental peanut exposure, by desensitising peanut-allergic children and adolescents to peanut allergen.
- The efficacy and safety of Palforzia were assessed in two Phase 3 placebo-controlled trials: PALISADE (ARC003) and ARTEMIS (ARC010). ARC004 is an open-label follow-on study to PALISADE.
- In the phase 3 trials, Palforzia treatment led to clinically meaningful desensitisation to peanut protein along with reduced symptom severity and reactions when patients were exposed to peanut:
  - The primary efficacy endpoint (ITT population, tolerating 1000 mg) was met in both RCTs with treatment differences (Palforzia-placebo) of 47.8% ($p<0.0001$) in PALISADE and 56.0% ($p<0.0001$) in ARTEMIS.
  - In both studies, approximately 63-68% of Palforzia-treated patients tolerated 600 mg and 74-77% tolerated 300 mg of Palforzia in the exit food challenge.
  - Patients in PALISADE and ARTEMIS experienced over 100-fold improvement in the amount of peanut they could tolerate.
  - In PALISADE and ARTEMIS, Palforzia significantly reduced not only the incidence but also the severity of allergic reactions during the exit DBPCFC.
  - Long-term follow-up of Palforzia patients for up to 2 years of treatment demonstrates that protection levels continue to improve over time, with approximately half of patients tolerating 2000 mg after 1.5 years treatment, rising to approximately 80% after 2 years treatment.
- Improvement in disease-related HRQoL has been demonstrated in patients who have been on Palforzia treatment for 18 months (up-dosing + 12 months of maintenance) in PALISADE and ARC004
- Gastrointestinal adverse events are the most frequently reported, which is expected due to the oral route of administration. Furthermore, their incidence reduces with duration of treatment.
- Overall, the safety profile of Palforzia in patients 4–17 years appears acceptable with no unexpected safety signals. There was a higher frequency of hypersensitivity reactions in Palforzia-treated participants, which is to be expected due to the immunomodulatory effect of Palforzia.

B.2.1 Identification and selection of relevant studies

Clinical studies relevant to this submission were identified in a systematic literature review (SLR), which was designed to identify RCTs that evaluated the efficacy and safety of Palforzia versus standard of care (SoC) in children with peanut allergy. Currently, the SoC comparator is peanut avoidance, symptomatic and emergency medication, as per the scope.

Since Palforzia is a newly licensed treatment with no active comparators, no observational or real-world studies have been conducted to date, hence the search was initially restricted to RCTs.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

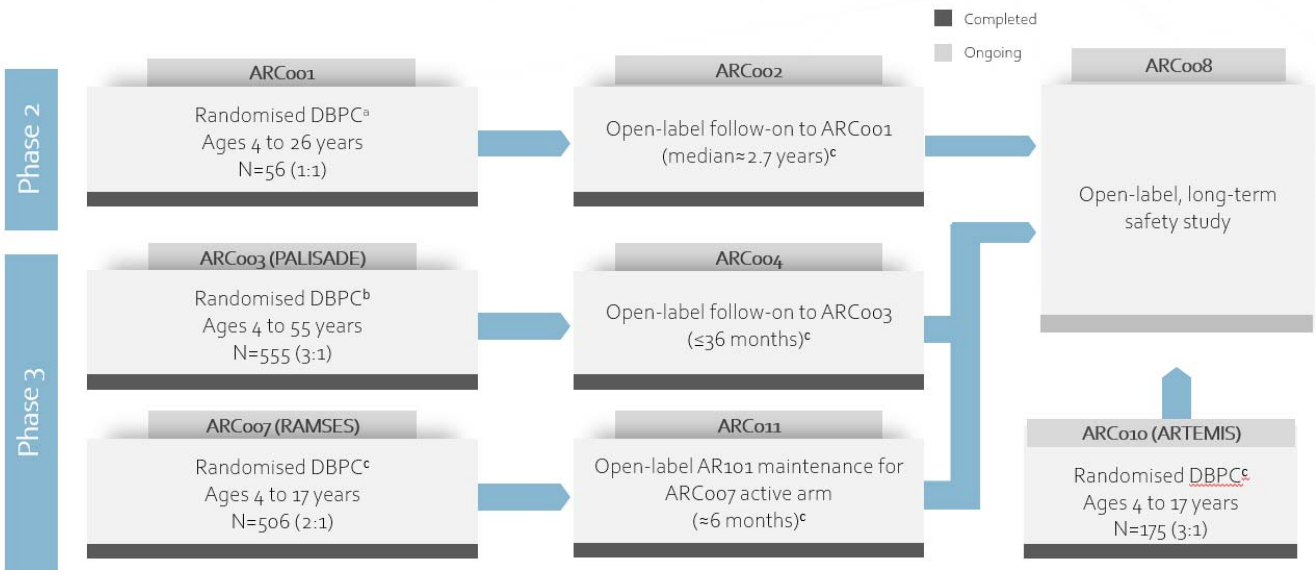
B.2.2 List of relevant clinical effectiveness evidence

In total, two relevant RCTs were identified: two Phase 3 trials reporting evidence for Palforzia: PALISADE (ARC003) and ARTEMIS (ARC010).[37,38] In addition, the search also identified an open-label follow-on study to the PALISADE study (ARC004).[64] Another two Phase 3 trials (RAMSES [ARC007] as well as its respective open label extension study ARC011) were excluded since they only assessed safety and tolerability, not efficacy, and were conducted only in the United States (see Section 2.10.1 for information on pooled safety analysis). Two Phase 2 studies were also identified (ARC001 and its open-label extension study ARC002); these were not included in the cost-effectiveness model nor the SmPC since both trials were Phase 2, relatively small in number (N=55 in ARC001 and N=47 in ARC002) and conducted only in the United States. The results of both studies were consistent with those obtained in the Phase 3 trials and do not add greater insight regarding the efficacy of Palforzia in a meaningful way. They are therefore not discussed further.

Finally, ARC008 is an ongoing open-label extension study for patients continuing on Palforzia treatment after rolling over from ARC002, ARC004, ARC010, ARC007 and ARC011. The objective of ARC008 is to provide ongoing safety monitoring and continuity of Palforzia treatment pending commercial availability. As an ongoing, unpublished safety-only study, interim results are discussed briefly in the safety section B.2.10 only.

Figure 7 illustrates the Palforzia clinical trial programme as a whole.

Figure 7. Palforzia clinical trial programme



DBPC: double-blind, placebo-controlled
a ARC001 assessed efficacy (desensitisation to 300 mg of peanut protein) and safety.
b ARC003 (PALISADE) assessed efficacy (desensitisation to 600 mg peanut protein (North America) and 1000 mg peanut protein (Europe)) and safety.
c ARC002, ARC004, ARC007 (RAMSES) and ARC011 assessed safety.
d ARC010 (ARTEMIS) assessed efficacy (desensitisation to 1000 mg peanut protein) and safety.
Source: Aimmune Therapeutics data on file.

An overview of the two relevant RCTs identified, PALISADE (ARC003) and ARTEMIS (ARC010), and the follow-on study ARC004 is presented in Table 4.

Table 4: Clinical effectiveness evidence

Study	ARC003 (PALISADE), NCT02635776		ARC004 (PALISADE follow-on), NCT02993107		ARC010 (ARTEMIS), NCT03201003	
Study design	Phase 3 international, randomised, double-blind, placebo-controlled trial		Open-label follow-on study of the phase 3 PALISADE study		Phase 3 international, randomised, double-blind placebo-controlled trial	
Population	Participants aged 4 to 55 years with a clinical history of allergy to peanuts or peanut-containing foods		Participants aged 4 to 55 years who completed the PALISADE (ARC003) study		Participants aged 4 to 17 years with a clinical history of allergy to peanuts or peanut-containing foods	
Intervention(s)	Palforzia + avoidance *See Table 5 for dosing regimen*		Palforzia + avoidance *See Table 5 for dosing regimens*		Palforzia + avoidance *See Table 5 for dosing regimen*	
Comparator(s)	Placebo + avoidance *See Table 5 for dosing regimen*		Not applicable		Placebo + avoidance *See Table 5 for dosing regimen*	
Indicate if trial supports application for marketing authorisation	Yes	X	Yes	X	Yes	X
	No		No		No	
Indicate if trial used in the economic model	Yes	X (patients aged 4-17 only)	Yes	X (patients aged 4-17 at beginning of ARC003, once daily dosing Cohorts 1 and 3A only)	Yes	X
	No		No		No	
Rationale for use/non-use in the model	PALISADE is a pivotal clinical trial supporting the EMA regulatory submission and the approved indication for Palforzia. The trial provides comparative evidence for Palforzia versus placebo		This follow-on trial provides information on safety and sustained efficacy and supports the EMA regulatory submission, as per the SmPC. The trial provides longer term data and confirms the long-term efficacy of daily dosing.		ARTEMIS is a pivotal clinical trial supporting the EMA regulatory submission and the approved indication for Palforzia. The trial provides comparative evidence for Palforzia versus placebo	
Reported outcomes specified in the decision problem	• **Peanut allergy desensitisation** • **Systemic allergic reactions (including anaphylaxis)**		• **Adverse effects (AEs) of treatment** • **Peanut allergy desensitisation**		• **Peanut allergy desensitisation** • **Systemic allergic reactions (including anaphylaxis)**	

Bold outcomes are included in the base case economic model	• **Frequency and severity of symptoms after accidental exposure to peanut** • **Treatment discontinuation** • **Adverse effects (AEs) of treatment** • Health-related quality of life *Notes:* *1. Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively) and 1000 mg (2043 mg cumulatively) peanut protein in an exit double-blind placebo-controlled food challenge (DBPCFC) (see Table 6).* *2.Patient-level data were used to populate the economic model (see Section B.3)* *3. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.* *4. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment with and without adrenaline" in this dossier*	• **Systemic allergic reactions (including anaphylaxis)** • Frequency and severity of symptoms after accidental exposure to peanut • **Treatment discontinuation** • Health-related quality of life *Notes:* *1. The term "Adverse events" is used in this dossier rather than "Adverse effects".* *2. Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively), 1000 mg (2043 mg cumulatively) and 2000 mg (4043 mg cumulatively) peanut protein in an exit DBPCFC (see Table 6).* *3. Patient-level data were used to populate the economic model (see Section B.3)* *4. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.* *5. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment*	• **Frequency and severity of symptoms after accidental exposure to peanut** • **Treatment discontinuation** • **Adverse effects (AEs) of treatment** • Health-related quality of life *Notes:* *1. Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively) and 1000 mg (2043 mg cumulatively) peanut protein in an exit DBPCFC (see Table 6).* *2. Patient-level data were used to populate the economic model (see Section B.3)* *3. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.* *4. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment with and without adrenaline" in this dossier* *5. The term "Adverse events" is used in this dossier rather than "Adverse effects".*

	5. The term "Adverse events" is used in this dossier rather than "Adverse effects". *6. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3.4.4)*	*with and without adrenaline" in this dossier* *6. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3.4.4)*	*6. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3.4.4)*
All other reported outcomes	Efficacy outcomes: • The maximum symptom severity in participants aged 4 to 17 years that occurred at any challenge dose of peanut protein during the exit DBPCFC • The proportion of participants aged 18 to 55 years who tolerated a single highest dose of at least 1000 mg of peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC • Maximum dose achieved with no or mild symptoms at exit • The change from baseline in single highest tolerated dose of peanut protein at DBPCFCs • The use of adrenaline as rescue medication at the exit DBPCFC • Changes in peanut-specific serum IgE and IgG4 levels • Changes in peanut skin prick test diameter • Treatment satisfaction as assessed by the TSQM-9 questionnaire	Efficacy outcomes: • The use of adrenaline as rescue medication • Single highest tolerated dose and change from baseline at the maintenance and exit DBPCFCs • Maximum severity of symptoms at each challenge dose at the maintenance and exit DBPCFCs • Treatment satisfaction as assessed by the TSQM-9 questionnaire • Changes in peanut-specific IgE and IgG4 levels • Changes in peanut skin prick test wheal diameter Safety outcomes: • Assessment of asthma control using the Asthma Control Test questionnaire in participants with asthma *Note: since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is*	Efficacy outcomes: • The maximum symptom severity that occurred at any challenge dose of peanut protein during the exit DBPCFC • Maximum dose achieved with no or mild symptoms at exit • The change from baseline in single highest tolerated dose of peanut protein at DBPCFCs • The use of adrenaline as rescue medication at the exit DBPCFC • Changes in peanut-specific serum IgE and IgG4 levels • Changes in peanut skin prick test diameter • Treatment satisfaction as assessed by the TSQM-9 questionnaire and exit questionnaire • Use of adrenaline as rescue medication during initial dose escalation, up-dosing and maintenance (by age group) Safety outcomes:

	Safety outcomes: • Assessment of asthma control using the Asthma Control Test in participants with asthma (by age group) *Note: since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint (see Section 2.6.1).*	*used as a surrogate endpoint (see Section 2.6.2).*	• Assessment of asthma control using the Asthma Control Test in participants with asthma (by age group) *Note: since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint (see Section 2.6.3).*

AE: adverse events; DBPCFC: double-blind placebo-controlled food challenge; EMA: European Medicines Agency; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy-Related Quality of Life Questionnaire; IgE: immunoglobulin E; IgG4: immunoglobulin G4; NHLBI: National Heart, Lung, and Blood Institute; SmPC: Summary of Product Characteristics; TSQM-9: Treatment Satisfaction Questionnaire for Medication
Sources: Vickery et al., 2018[38]; Vickery et al. 2020[64]; Hourihane et al. 2020[37]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Please see Table 5 for the comparative summary of trial methodology for the two Phase 3 studies (PALISADE and ARTEMIS) and the PALISADE follow-on study (ARC004).

Table 5: Comparative summary of trial methodology

Trial number (acronym)	ARC003 (PALISADE)[38]	ARC004 (PALISADE follow-on)[64-67]	ARC010 (ARTEMIS)[37]
Location	66 sites in 10 countries (Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom, United States)	65 sites in 9 countries (Canada, Germany, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom, United States)	18 sites in 7 countries in Europe (France, Germany, Ireland, Italy, Spain, Sweden, United Kingdom)
Trial design	Phase 3, international, randomised (3:1), double-blind, placebo-controlled study	Open-label follow-on study to PALISADE	Phase 3, international, randomised (3:1), double-blind, placebo-controlled study
Eligibility criteria for participants	Participants aged 4 to 55 years with a clinical history of peanut allergy and a serum IgE to peanut of ≥0.35 kUA/L or a skin prick test to peanut of ≥3 mm compared with control at the time of screening *Note: only participants aged 4 to 17 years, per the labelled indication of Palforzia, were used to populate the economic model.* *See Table 7 for full inclusion/exclusion criteria*	Participants who successfully completed the ARC003 study and were either assigned to treatment with Palforzia and tolerated the 300-mg dose at the exit DBPCFC or were assigned to the placebo arm who completed the exit DBPCFC. *Note: to reflect licensed dosing only participants from cohort 1 and 3A (aged 4 to 17 years) from group 2 were used to populate the economic model.*	Participants aged 4 to 17 years with a clinical history of peanut allergy and a serum IgE to peanut of ≥0.35 kUA/L and/or a peanut skin prick test mean wheal diameter ≥3 mm compared with control at the time of screening *See Table 12 for full inclusion/exclusion criteria*
Settings and locations where the data were collected	• The first dose at each new dose level and the first dose of each kit issued during maintenance (every 4 weeks) were administered at the study site (physician's office). • Daily dosing continued at home • Double-blind placebo-controlled food challenges (DBPCFCs) were conducted at the study site during the screening and exit visits • Laboratory evaluations were conducted at the study site during the screening visit, at the end of the up-dosing period,	As per PALISADE	As per PALISADE, with the following exception: • Skin prick tests were conducted at the study site during the screening visit, at the end of the up-dosing period, at the exit visit and during any unscheduled visit.

	at the exit visit and during any unscheduled visit • Skin prick tests were conducted at the study site during the screening visit, at the end of the up-dosing period, and at the exit visit • FAQLQ and FAIM questionnaires were completed at the study site during the screening and exit visits • AE and allergy symptom monitoring were conducted at the study sites during all scheduled or unscheduled study visits • Daily dosing and reactions to home administration were documented in diaries, which were reviewed by study staff during study site visits		

Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Palforzia: n=416 Placebo: n=139 • Randomisation by interactive online system. • Day 1 of initial dose escalation: participants received escalating doses of Palforzia (0.5-6 mg) or placebo at 20- to 30-minute intervals at the study site and were observed for at least 90 minutes after completion of dose escalation • Day 2: tolerability of 3 mg Palforzia or placebo was confirmed • Up-dosing: participants received escalating doses from 3 to 300 mg/day Palforzia or placebo at 2-week intervals as tolerated (20-40 weeks) • Maintenance: participants who tolerated 300 mg/day Palforzia or placebo continued dosing at 300 mg/day (approximately 24-28 weeks) • The first dose at each new dose level and the first dose of each kit issued during maintenance (every 4 weeks) were administered at the study site (physician's office). • Daily dosing continued at home • Study product doses could be reduced, held, or withheld due to AEs or allergy symptoms at investigator discretion. • The total duration of treatment: approximately 12 months Matching capsules or sachets containing Palforzia or placebo were emptied into	Palforzia: n=358 • Group 1 (placebo-treated participants in ARC003) n=102: participants received Palforzia during initial dose escalation (day 1: 0.5 to 3 or 6 mg; day 2: 3 mg), up-dosing (3-300 mg/day for 22-40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24-28 weeks). Participants who tolerated a single highest dose of ≥300 mg in the DBPCFC after 24-28 weeks of maintenance, could receive Palforzia during extended maintenance. The total duration of Palforzia treatment in group 1 was 88 to 136 weeks. • Group 2 (Palforzia-treated participants who tolerated ≥300 mg peanut protein in the exit DBPCFC in ARC003) n=256: participants directly entered the extended maintenance period and were assigned to 1 of 3 sequential dose cohorts. o Cohort 1: The first approximately 120 participants received 300 mg/day (once daily, OD) for 28 weeks; n=112. o Cohort 2: The next approximately 50 participants received 300 mg every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks; n=48. o Cohort 3: All remaining participants were assigned to 1 of 3 dosing regimens in cohort 3:	Palforzia: n=132 Placebo: n=43 • Randomisation by proprietary interactive web response system • Description, dosing and administration of study drugs were as in PALISADE, with the following difference: • Maintenance: participants who tolerated 300 mg/day Palforzia or placebo dosing at 300 mg/day (approximately 12 weeks). • The total duration of treatment: approximately 9 months • Permitted and prohibited medications were as in PALISADE, with the following exception: • The prohibited use of omalizumab was expanded to include any therapeutic immunomodulatory antibodies (e.g., omalizumab, mepolizumab, reslizumab, dupilumab) last used within 6 months of screening

	and mixed with a vehicle food (e.g., apple sauce, yogurt, pudding, or other palatable, age-appropriate, food). The volume of the vehicle food was to be such that the entire dose could be consumed in a few spoonfuls. The study product was to be consumed as promptly after mixing as practicable and each dose was to be consumed at a consistent time (within 4 hours) each day, with an interval of at least 8 hours between doses. <u>Permitted medications</u> • Current medications, including those for asthma, allergic rhinitis, and atopic dermatitis. • Topical steroids • Antihistamines or adrenaline for acute allergic reactions, along with IV fluids, beta-adrenergic agonists (e.g. albuterol), oxygen or steroids • Antihistamines and other medications that could interfere with the assessment of an allergic reaction were to be discontinued approximately 5 half-lives of the medication before the first day of initial dose escalation, skin prick tests, and DBPCFCs • The use of any medication with known cardiovascular side effects had to be weighed against the potential benefits of peanut OIT. Classes of drugs with a high potential for cardiovascular side effects include but were not limited to antipsychotics, cyclooxygenase 2 inhibitors (chronic use), nonsteroidal	• Cohort 3A: 300 mg/day for 56 weeks (n=31) • Cohort 3B: 300 mg/day for 4 weeks, QOD for 24 weeks, then BIW for 24 weeks (total of 56 weeks; n=31) • Cohort 3C: 300 mg/day for 4 weeks, QOD for 24 weeks, BIW for 24-56 weeks (total of 84 weeks; n=34) *See Figure 11 for ARC004 trial design schema* *Note: since ARC004 explored different dosing regimens of Palforzia, only the cohorts that remained on daily dosing in ARC004, per the labelled indication of Palforzia, were used to populate the economic model – i.e. Cohorts 1 and 3A.* **Administration of daily or non–daily dosing regimens was contingent on results; planned regimens were every other day, twice weekly, once weekly, or every other week. Regimens less frequent than twice weekly were not instituted because of small cohort size and at the recommendation of the Safety Monitoring Committee.* [redacted] [redacted]	

	anti-inflammatory drugs (chronic use), antiarrhythmics, antihypertensives, and antineoplastics. <u>Prohibited medications</u> • Omalizumab • Systemic (oral) corticosteroids used for more than 3 consecutive weeks throughout the study (if used, the study product dose must not have increased during the 3 days after discontinuation of oral steroids) • Oral beta-blockers • Angiotensin-converting enzyme inhibitors • Angiotensin-receptor blockers • Calcium channel blockers • Tricyclic antidepressants • Immunomodulatory/ immunosuppressive medications (eg, cyclosporine, tacrolimus, antitumour necrosis-alpha drugs, anti-IgE drugs)	[redacted]	
Primary outcomes (including scoring methods and timings of assessments)	**Peanut allergy desensitisation** • The proportion of participants who tolerated a single highest dose of at least 1000 mg of peanut protein (2043 mg cumulative) without dose-limiting symptoms (either no or mild symptoms) at the exit DBPCFC* • Dose-limiting symptoms are any symptoms that, in the investigator's assessment, indicate poor tolerability of the last challenge dose administered and preclude safe advancement to the next challenge dose	• The incidence of [redacted] adverse events • Treatment-emergent adverse events were defined as [redacted]	**Peanut allergy desensitisation**: • The proportion of participants who tolerated a single highest dose of at least 1000 mg of peanut protein (2043 mg cumulative) without dose-limiting symptoms (either no or mild symptoms) at the exit DBPCFC • Dose-limiting symptoms are any symptoms that, in the investigator's assessment, indicate poor tolerability of the last challenge dose administered and preclude safe advancement to the next challenge dose.

	• Increasing amounts of peanut protein (not Palforzia) or placebo (oat flour) were mixed in a vehicle food and administered at 20- to 30-minute intervals. Both the peanut and placebo challenge materials were matched for consistency and taste. The peanut and placebo DBPCFCs were conducted on separate days (within 7 days) and assigned in random order. DBPCFCs were performed at screening/baseline and exit visits. *Analysis was limited to participants aged 4 to 17 years* *Note: Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively) and 1000 mg (2043 mg cumulatively) peanut protein in the exit DBPCFC) (see Table 6).*	 *Analysis was limited to participants aged 4 to 17 years*	• Increasing amounts of peanut protein (not Palforzia) or placebo (oat flour) were mixed in a vehicle food and administered at 20- to 30-minute intervals. Both the peanut and placebo challenge materials were matched for consistency and taste. The peanut and placebo DBPCFCs were conducted on separate days (within 7 days) and assigned in random order. DBPCFCs were at screening/baseline and exit visits. *Note: Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively) and 1000 mg (2043 mg cumulatively) peanut protein in a DBPCFC (see Table 6).*
Other outcomes used in the economic model/ specified in the scope	Efficacy outcomes: • Frequency and severity of symptoms after accidental exposure to peanut • Health-related quality of life for participants by both self- and caregiver proxy report (measured by FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales) Safety outcomes:	Efficacy outcomes: • Peanut allergy desensitisation • Frequency and severity of symptoms after accidental exposure to peanut • Health-related quality of life for participants by both self- and caregiver proxy report (measured by FAQLQ and FAIM scales) Safety outcomes: • Systemic allergic reactions (including anaphylaxis)	Efficacy outcomes: • Frequency and severity of symptoms after accidental exposure to peanut • Health-related quality of life for participants by both self- and caregiver proxy report (measured by FAQLQ and FAIM scales) Safety outcomes: • Systemic allergic reactions (including anaphylaxis) • Treatment discontinuation

	• Systemic allergic reactions (including anaphylaxis) • Treatment discontinuation • Adverse effects (AEs) of treatment *Notes:* *1. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment with and without adrenaline" in this dossier.* *2. Since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint (see Section 2.6.1).* *3. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3).* *4. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.* *5. The term "Adverse events" is used in this dossier rather than "Adverse effects".*	• Treatment discontinuation *Notes:* *1. The term "Adverse events" is used in this dossier rather than "Adverse effects".* *2. Peanut allergy desensitisation was evaluated by challenge doses of <300 mg (<443 mg cumulatively), 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively), 1000 mg (2043 mg cumulatively) and 2000 mg (4043 mg cumulatively) peanut protein in the exit DBPCFC (see Table 6).* *3. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment with and without adrenaline" in this dossier.* *4. Since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint (see Section 2.6.2).* *5. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3)* *6. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.*	• Adverse effects (AEs) of treatment *Notes:* *1. "Frequency and severity of symptoms after accidental exposure to peanut" are referred to as "Accidental exposure to peanut requiring treatment with and without adrenaline" in this dossier.* *2. Since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint (see Section 2.6.3).* *3. HRQoL as assessed by FAQLQ and FAIM was collected during the trials but not used in the model (see Section B.3)* *4. The term "anaphylactic reactions" is used in this dossier to indicate systemic allergic reactions of any severity (including anaphylaxis); "anaphylaxis" is used to indicate severe systemic allergic reactions.* *5. The term "Adverse events" is used in this dossier rather than "Adverse effects".*
Pre-planned subgroups	• By geographic region (North America and Europe) in paediatric participants aged 4 to 17 years	• [redacted]	• By paediatric age group (children aged 4 to 11 years and adolescents aged 12-17 years)

	• By paediatric age group (children aged 4 to 11 years and adolescents aged 12 to 17 years) • By geographic region and paediatric age group (North America children, North America adolescents, Europe children, Europe adolescents) *Note: subgroup analyses were conducted for the ITT and completer populations*		• By country

AE: adverse events; BIW: twice weekly; CTCAE: Common Terminology Criteria for Adverse Events; DBPCFC: double-blind placebo-controlled food challenge; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy-Related Quality of Life Questionnaire; HRQoL: health-related quality of life; IgE: immunoglobulin E; IgG4: immunoglobulin G4; ITT: intention-to-treat; OIT: oral immunotherapy; OD: once daily; QOD: every other day; QW: once weekly

*NB It should be noted that the trial publication states primary efficacy endpoint as 'The proportion of participants who tolerated a single highest dose of at least 600 mg of peanut protein. This is due to a difference between the North American and the European primary endpoint. The data in this dossier are represented using the European primary efficacy endpoint of 1000 mg.

2.3.1 Overview of the DBPCFC as a measure of clinical efficacy

Without an allergen trigger, peanut-allergic patients do not suffer physical symptoms, therefore a benefit assessment of Palforzia therapy requires induction of a response via an oral food challenge. The DBPCFC is a model that simulates accidental exposure to selected food allergens and, as such, acts as a surrogate endpoint to determine tolerance, thereby allowing for the clinical assessment of the patient's response.

The DBPCFC model was utilised in the Palforzia clinical trial development programme to determine an individual patient's ability to tolerate peanut protein, and it has been utilised in previous OIT trials .[68] To date there is no other available or validated test to measure efficacy of an OIT in the clinical setting, and it has been accepted by the regulatory agencies as a robust, reliable, and clinically meaningful endpoint.[69]

The DBPCFC is performed in medically supervised settings. During the DBPCFC, allergic patients are exposed to gradually increasing doses of the allergen to which they are allergic, generally in half-log increments, starting at 1 mg. The test is stopped when a challenge dose elicits an allergic reaction (dose-limiting symptoms described below) as assessed by a trained observer. The DBPCFC procedure is repeated with both peanut protein and a placebo.

Defatted peanut powder was used in DBPCFCs performed in Aimmune clinical studies following the PRACTALL guidelines.[70] The Palforzia clinical trials employed one modification to the PRACTALL guidelines, which was the addition of a dose of 600 mg peanut protein during the exit DBPCFC (administered between the 300 mg and 1000 mg dose levels, see Table 6**Error! Reference source not found.**).

Table 6: Modified PRACTALL DBPCFC doses using peanut flour with 50% peanut protein content at screening and exit DBPCFC

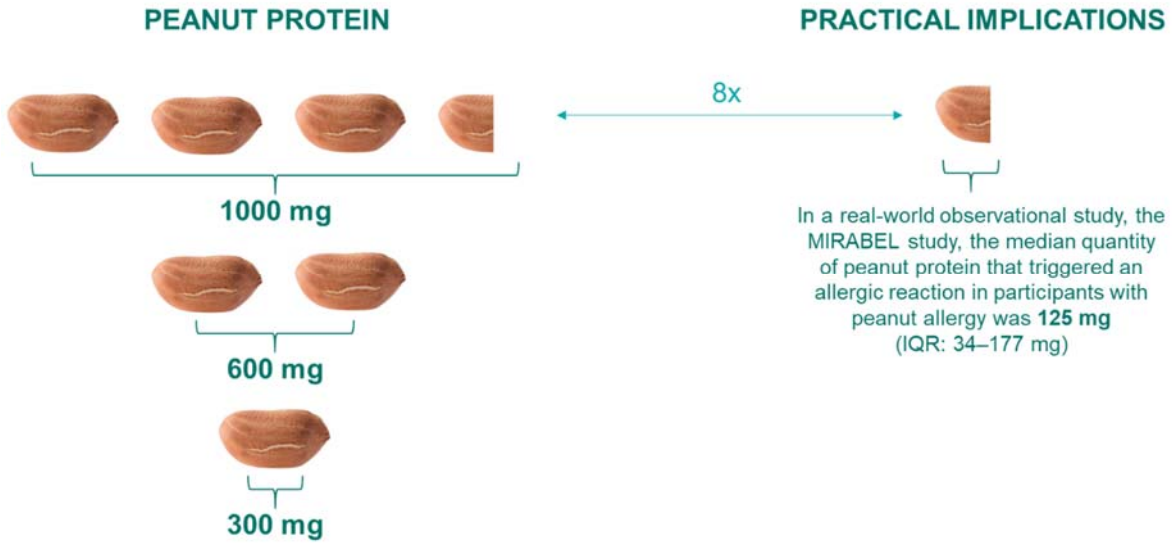
	Challenge doses (administered at 20–30-minute intervals)		
	Amount of peanut protein at each challenge dose (mg)	Cumulative amount of peanut protein (mg) at Screening	Cumulative amount of peanut protein (mg) at Exit
Screening only*	1	1	0 (or 1)*
Screening and Exit	3	4	3 (or 4)*
Screening and Exit	10	14	13 (or 14)*
Screening and Exit	30	44	43 (or 44)*
Screening and Exit	100	144	143 (or 144)*

Exit only	300	-	443 (or 444)*
Exit only	600	-	1043 (or 1044)*
Exit only	1000	-	2043 (or 2044)*
Exit only†	2000	-	4043 (or 4044)*

*Participants who failed their Screening DBPCFC at the 1-mg challenge dose of peanut protein were required to start the Exit DBPCFC with a 1-mg dose. At the investigator's discretion, a 1-mg dose could be added at the beginning of the escalation of any participant's Exit DBPCFC.
†The 2000-mg dose was only used in ARC004

The 1000 mg dose level, corresponding to approximately 3 to 4 peanut kernels[28] (Figure 8Figure 8) and used as the primary efficacy endpoint in both PALISADE and ARTEMIS trials, provides protection with an approximately 8-fold margin over the median estimated real-world eliciting dose of 125 mg peanut protein (approximately ½ of a peanut kernel) observed in the MIRABEL real-world observational study conducted in Europe.[27]

Figure 8: Peanut kernel equivalence



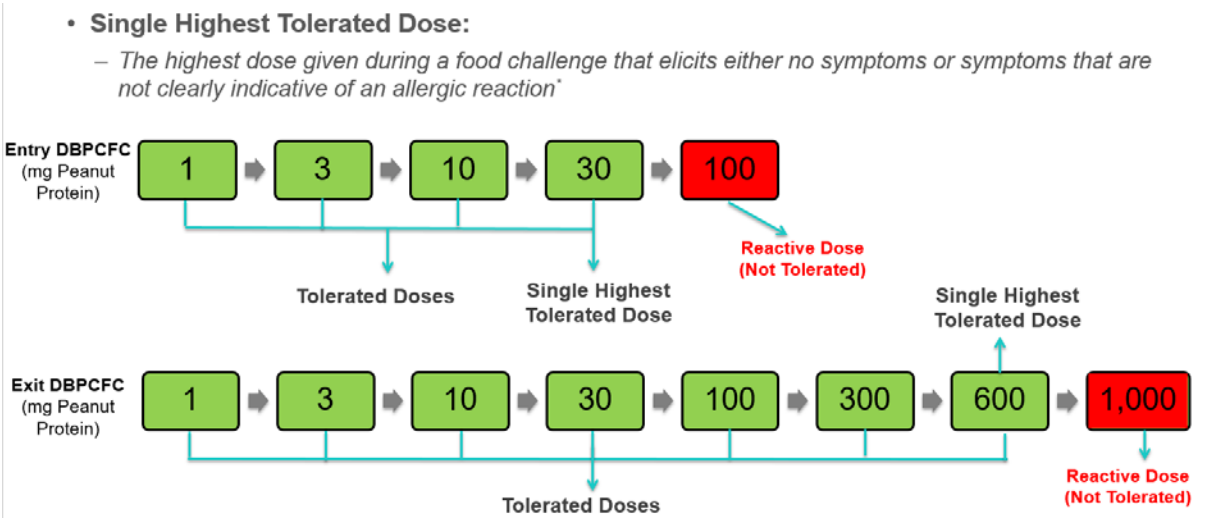
IQR: interquartile range
Source: Hourihane et al., 2020[37]; Vickery et al., 2018[38]; Deschildre et al., 2016[27]

Overall, the efficacy of a desensitisation treatment is evaluated based on dose-limiting symptoms and a defined tolerability threshold. Patient-relevant dose-limiting symptoms in the Palforzia clinical programme were defined as any symptoms that, in the investigator's assessment, indicated poor tolerability of the last challenge dose administered and precluded advancement to the next challenge dose. The tolerability threshold is the highest dose tolerated during the DBPCFC that did not elicit dose-

limiting symptoms (Figure 9). The efficacy of peanut OIT is commonly investigated using the tolerability threshold.[71-73]

Evaluating the desensitisation of an OIT based on DBPCFC and a defined tolerability threshold thus enables a clear demonstration of the clinical benefit of Palforzia, leading to a state of clinically meaningful and patient-relevant desensitisation to peanut, and a reduction of the incidence and severity of allergic reactions upon exposure to peanut protein.

Figure 9: Single highest tolerated dose terminology used in DBPCFC



DBPCFC: double-blind, placebo-controlled food challenge
*For the tolerated dose, the symptoms should not be any worse than mild, often without objective signs, are usually transient, and typically subjective (e.g., pruritus of the skin, nausea, throat/abdominal discomfort, etc).
Source: Adapted from EpiMetrix Inc., 2018[74]

2.3.2 PALISADE (ARC003)

Trial design

PALISADE was a Phase 3, international, randomised (3:1), double-blind, placebo-controlled study to evaluate the efficacy and safety of Palforzia OIT for the treatment of peanut allergy. The primary objective was to demonstrate the efficacy of Palforzia through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children aged 4 to 17 years.[38] Please see trial design details in Table 5 and Figure 10.

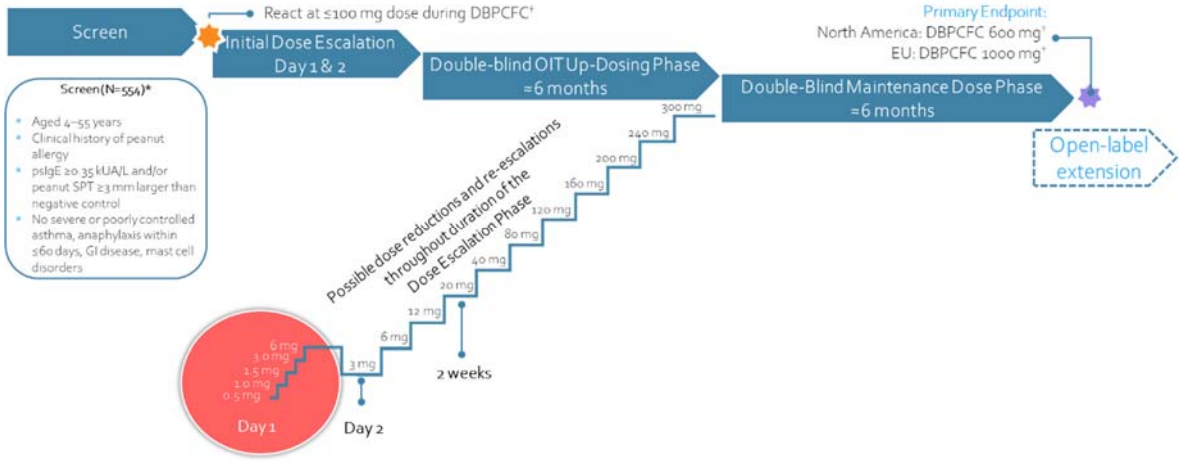
The study planned to enrol 500 participants aged 4 to 55 years with peanut allergy, including 495 participants 4 to 17 years of age. Participants were required to have allergic dose-limiting symptoms at a challenge dose of 100 mg or less of peanut protein in a DBPCFC at screening. During the challenge, increasing amounts of peanut

protein (not Palforzia) or placebo (oat flour) were mixed in a vehicle food and administered at 20- to 30-minute intervals (Table 6).[38]

Participants were randomised in a 3:1 ratio to either the Palforzia or placebo arms (double-blinded). Randomisation was performed using an interactive online system according to a central randomisation schedule of randomly permutated blocks. Randomisation was stratified by geographic region (North America and Europe) and age (children aged 4 to 17 years and adults aged 18 to 55 years).[38]

The trial design schema is presented in Figure 10.

Figure 10: PALISADE (ARC003) trial design schema



DBPCFC: double-blind, placebo-controlled food challenge; GI: gastrointestinal; OIT: oral immunotherapy; psIgE, serum peanut-specific immunoglobulin E; SPT: skin prick test.
Entry and exit DBPCFCs were conducted by a blinded assessor. * Prophylactic medication use was not allowed during the trial.
† Dose of peanut protein.
Source: Adapted from Vickery et al. 2018.[38]

Eligibility criteria

PALISADE enrolled peanut-allergic participants aged 4 to 55 years. Detailed eligibility criteria are presented in Table 7.

Table 7: PALISADE (ARC003) eligibility criteria

Study (acronym)	ARC003 (PALISADE)
Inclusion criteria	• Participants aged 4 to 55 years • Clinical history of allergy to peanuts or peanut-containing foods • Serum IgE to peanut ≥0.35 kUA/L (determined by a commercial test system, ImmunoCAP, [formerly UniCAP], within the past 12 months) and/or a skin prick test to peanut ≥3 mm compared with control • Experience dose-limiting symptoms to a single dose of peanut protein ≤100 mg at the screening DBPCFC • Use of effective birth control by female participants of childbearing potential

	• Not residing at the same address as another subject in this or any peanut OIT study
Exclusion criteria	• History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension • History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of the screening DBPCFC • History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that was, or was at significant risk of becoming, unstable or required a change in chronic therapeutic regimen • History of eosinophilic oesophagitis, other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease, symptoms of dysphagia (e.g., difficulty swallowing, food getting stuck), or recurrent gastrointestinal symptoms of undiagnosed etiology • Current participation in another interventional study • Subject was in build-up phase of immunotherapy to another allergen (i.e., has not reached maintenance) • Severe asthma (2007 NHLBI criteria steps 5 or 6) • Mild or moderate asthma (2007 NHLBI criteria steps 1-4), if uncontrolled or difficult to control • History of steroid medication use • Inability to discontinue antihistamines 5 half-lives of the medication before the initial day of escalation, skin prick testing, or DBPCFC • Lack of an available palatable vehicle food to which the subject is not allergic • Use of any therapeutic antibody, any investigational peanut immunotherapy or any other immunomodulatory therapy excluding corticosteroids within the past 6 months • Use of beta blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers • Pregnant or lactating • Residing in the same place as another subject in the study • Participation in another clinical trial within 30 days or 5 half-lives of the investigational product before randomisation, whichever was longer • Developed dose-limiting symptoms to the placebo part of the screening DBPCFC • History of a mast cell disorder • Allergy to oat • Hypersensitivity to adrenaline and any of the excipients of the product

DBPCFC: double-blind placebo-controlled food challenge; IgE: immunoglobulin E; NHLBI: National Heart, Lung, and Blood Institute; OIT: oral immunotherapy
Source: Vickery et al. 2018[38]

Settings and locations where data were collected

Details of the settings of data collection are presented in Table 5.

Briefly, PALISADE was conducted at 66 sites in 10 countries in Europe and North America: United Kingdom, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Canada and United States.[38]

Supervised administration of the first dose at each new dose level and the first dose of each kit issued during maintenance (every 4 weeks) occurred in a secondary/tertiary care setting. Daily dosing continued at home.[38]

Trial drugs and concomitant medication

Overall, 555 participants aged 4 to 55 years were enrolled in PALISADE, including 499 participants aged 4 to 17 years. In total, 372 participants aged 4 to 17 years received Palforzia and 124 received placebo.[38]

Trial treatment regimens and concomitant medication are detailed in Table 5. Trial medication was provided as matching capsules and sachets, administered after mixing into a matrix food to hide taste to ensure double-blinding.[38] Briefly, the trial was undertaken in three phases:

- **Dose-escalation phase** (2 days): participants received escalating doses of Palforzia (0.5 to 6 mg) or placebo at the study site, followed by observation for at least 90 minutes.[38,39]
- **Up-dosing phase** (20-40 weeks): participants received escalating doses of Palforzia (3 to 300 mg/day) or placebo at 2-week intervals.[38]
- **Maintenance phase** (24-28 weeks): participants received 300 mg/day of Palforzia or placebo.[38]

The total duration of treatment was approximately 12 months.[38]

Outcomes used in the economic model or specified in the scope, including the primary outcome

The outcomes of the PALISADE study were pre-specified. In participants aged 4 to 17 years with peanut allergy, the outcomes specified in the scope are:

Primary outcome

- **Peanut allergy desensitisation**: the proportion of participants who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulative) without dose-limiting symptoms.[38]

Key secondary outcomes

- The proportion of participants who could tolerate single doses of 300 mg and 600 mg at the exit DBPCFC[38]

Other outcomes

- Improvement in quality of life as measured by FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales.[38] Self-reported FAQLQ and FAIM were measured in participants aged 8 to 12 years and 13 to 17 years and parent proxy-reported FAQLQ and FAIM were measured in participants aged 4 to 12 years and 13 to 17 years. (See section B.2.6.4 and Table 61 in Appendix L for details on FAQLQ and FAIM assessments.[39])
- Frequency and severity of symptoms after accidental exposure to peanut (this outcome is referred to as "accidental exposure to peanut requiring treatment with and without adrenaline").[38] Since accidental exposures are uncommon, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate endpoint.

Please see Table 5 for details on the included outcomes.

Participant baseline characteristics

Among participants aged 4 to 17 years in PALISADE, baseline characteristics were well balanced between the trial arms and were consistent with those of children with peanut allergy in clinical practice (Table 8). Detailed characteristics are reported in Table 62 in Appendix L.

Table 8: **Key characteristics of participants aged 4 to 17 years across treatment groups in the ARC003 (PALISADE) study**

	Palforzia N=372	Placebo N=124	Total N=496
Age, years			

Median	9	9	9
4 to 11 years, n (%)	238 (64.0%)	89 (71.8%)	327 (65.9%)
12 to 17 years, n (%)	134 (36.0%)	35 (28.2%)	169 (34.1%)
Sex			
Male, n (%)	208 (55.9%)	76 (61.3%)	284 (57.3%)
Geographic region			
North America, n (%)	[redacted]	[redacted]	[redacted]
Europe, n (%)	[redacted]	[redacted]	[redacted]
Peanut-specific IgE (kUA/L)			
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Prick test mean wheal diameter (mm)			
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Non-peanut allergy history			
Allergic rhinitis, n (%)	[redacted]	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]	[redacted]
Atopic dermatitis, n (%)	[redacted]	[redacted]	[redacted]
Other food allergy, n (%)	[redacted]	[redacted]	[redacted]

BMI: body mass index; DBPCFC: double-blind placebo-controlled food challenge; IgE: immunoglobulin E; IgG4: immunoglobulin G4; Q: quartile.
Source: Vickery et al., 2018;[75] ARC003 Clinical study report[39]

Protocol changes

A number of major changes to the protocol affecting trial methods and outcomes occurred after trial commencement.[39,66] The full list of major protocol amendments is presented in Table 63 in Appendix L. The key changes were:

Table 9: **Key protocol changes in the ARC003 (PALISADE) study**

Protocol change	Rationale
Protocol Amendment 4 (Global) – 31 Jul 2017	
Changed the age range from 4 to 55 years to 4 to 17 years for primary and secondary objectives	[redacted]
Clarified that the age range was 4 to 17 years for primary and secondary endpoints, unless specified otherwise	
Separated the primary efficacy endpoint for North America and Europe	[redacted]
Changed the primary efficacy endpoint for Europe from tolerating a single highest dose of at least 600 mg to 1000 mg peanut protein	[redacted]
Separated the key secondary endpoints for North America and Europe	[redacted]

Added a new key secondary endpoint for North America: to measure the proportion of participants aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC	[redacted]
Modified key secondary endpoints for Europe	[redacted]
Added an endpoint to measure the proportion of participants aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC:	
Modified the last key secondary endpoint to include an age group: The proportion of participants aged 18 to 55 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC	
Modified exploratory endpoints	
Added an exploratory endpoint to repeat the primary efficacy endpoints in the following 3 age groups: 4 to 11 years, 12 to 17 years, and 4 to 55 years	[redacted]
Added an exploratory endpoint to repeat the first 3 key secondary endpoints and all other secondary endpoints in the following 4 age groups: 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years	

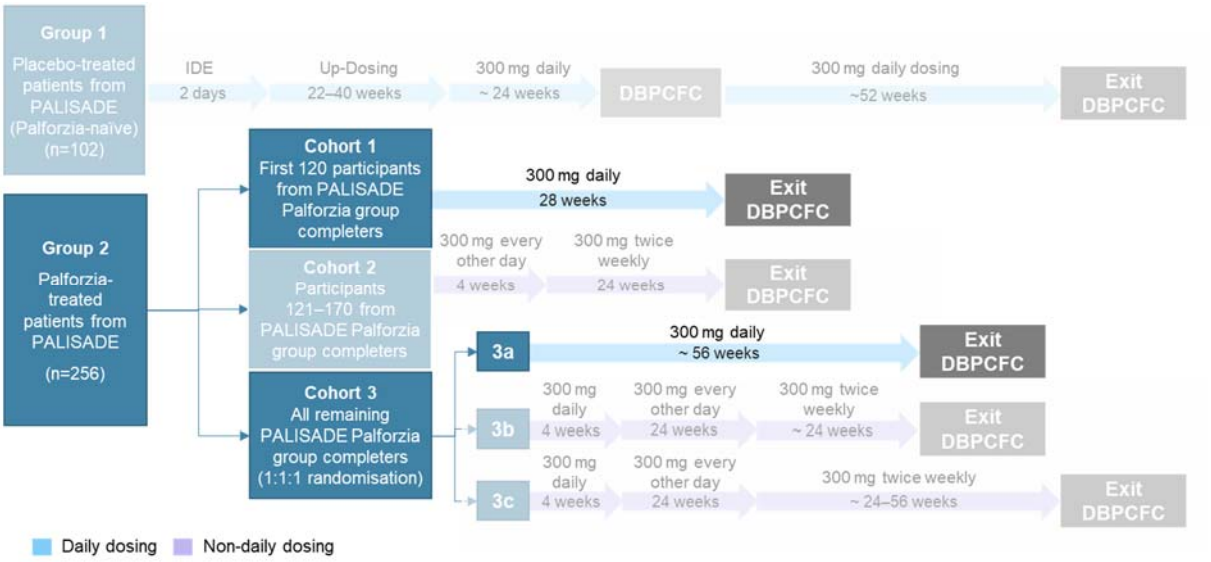
DBPCFC: double-blind placebo-controlled food challenge; EMA: European Medicines Agency; FDA: US Food and Drug Administration
Source: ARC003 Clinical study report[39]; Palforzia EPAR report[66]; Aimmune Therapeutics data on file.

2.3.3 PALISADE follow-on (ARC004)

Trial design

ARC004 is an open-label extension to the PALISADE phase 3, international, randomised, double-blind, placebo-controlled study.[64] Trial design details are presented in Table 5 and Figure 11.

Figure 11: PALISADE follow-on (ARC004) trial design schema



DBPCFC: double-blind placebo-controlled food challenge; IDE: initial dose escalation.
Source: Adapted from Vickery et al., 2020[64]

Over the course of both the PALISADE primary and follow-on studies, participants in Cohort 1 and Cohort 3A received 300 mg daily Palforzia maintenance treatment for approximately 13 months and 20 months, respectively.[64]

Eligibility criteria

Participants with peanut allergy who successfully completed the PALISADE study and either were assigned to treatment with Palforzia and tolerated the 300 mg dose at the exit DBPCFC, or were assigned to the placebo arm could opt to enrol into the PALISADE follow-up study. Female participants of childbearing potential were required to continue use of effective birth control.[64]

Complete inclusion and exclusion criteria for the PALISADE population are described in Table 7.

Settings and locations where data were collected

Details of the settings of data collection are presented in Table 5.

Trial drugs and concomitant medication

Please see Table 5 for details on trial drugs and concomitant medication.

Briefly, allocation of participants in the PALISADE follow-on study depended on the treatment previously received in the PALISADE study. Participants from the placebo

arm of the PALISADE trial underwent initial dose escalation, followed by up-dosing for 22 to 40 weeks, and maintenance dosing at 300 mg/day for approximately 24 weeks. Participants who received Palforzia in the PALISADE study were sequentially enrolled into one of five cohorts. Cohorts 1 and 3A continued receiving 300 mg/day of Palforzia for 28 weeks and approximately 56 weeks, respectively. Cohorts 2, 3B and 3C received non-daily dosing.[64]

Only the cohorts from the PALISADE active treatment arm that remained on daily dosing in ARC004, per the labelled indication of Palforzia, were used to populate the economic model (Cohorts 1 and 3A).

Outcomes used in the economic model or specified in the scope, including the primary outcome

The outcomes of the PALISADE follow-on study were pre-specified. In participants aged 4 to 17 years with peanut allergy, the outcomes were:

Primary outcome:

- The incidence of treatment-related adverse events and serious adverse events during the overall study period.[66]

Key secondary outcomes:

- Key events of anaphylactic reactions, adrenaline use, adverse events that led to discontinuation, certain gastrointestinal events including eosinophilic oesophagitis (EoE), accidental food allergen exposures, and asthma control in participants with asthma[64]
- Frequency and severity of symptoms after accidental exposure to peanut (this outcome is referred to as “accidental exposure to peanut requiring treatment with and without adrenaline”).[64] Since accidental exposures are very rare, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate endpoint.

Other outcomes:

- Peanut allergy desensitisation: the proportion of participants who tolerated a single highest dose of at least 300 mg (443 mg cumulative), 600 mg (1043 mg

cumulative), 1000 mg (2043 mg cumulative) and 2000 mg (4043 mg cumulative) with no more than mild symptoms at the exit DBPCFC

- Quality of life measures assessed by the FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales (patient- and parent-proxy reported)[66]

Please see Table 5 for details on the included outcomes.

Participant baseline characteristics

The key baseline characteristics of participants aged 4 to 17 years who received daily dosing regimens are presented in Table 10. Detailed participant characteristics are presented in Table 65 in Appendix L.

Table 10: **Key characteristics of participants aged 4 to 17 years who received daily dosing regimens across treatment groups in the ARC004 (PALISADE follow-on) study**

	Palforzia Cohort 1 (~28 weeks) N=112	**Palforzia Cohort 3A (~56 weeks) N=31**
Age, years		
Median	11	9
4 to 11 years, n (%)	[redacted]	[redacted]
12 to 17 years, n (%)	[redacted]	[redacted]
Sex		
Male, n (%)	57 (52.3%)	17 (54.8%)
Geographic region		
United States, n (%)	[redacted]	[redacted]
Canada, n (%)	[redacted]	[redacted]
United Kingdom, n (%)	[redacted]	[redacted]
Germany, n (%)	[redacted]	[redacted]
Spain, n (%)	[redacted]	[redacted]
Ireland, n (%)	[redacted]	[redacted]
Sweden, n (%)	[redacted]	[redacted]
Italy, n (%)	[redacted]	[redacted]
Netherlands, n (%)	[redacted]	[redacted]
Peanut-specific IgE (kUA/L)		
Median (Q1, Q3)	63.5 (20.9, 247.5)	45.4 (2.73, 220.5)
Prick test mean wheal diameter (mm)		
Median (Q1, Q3)	7.5 (5.5-10.0)	7.0 (4.0-9.5)
Non-peanut allergy history		
Allergic rhinitis n (%)	79 (72.5%)	20 (64.5%)

Asthma n (%)	47 (43.1%)	14 (45.2%)
Atopic dermatitis n (%)	67 (61.5%)	22 (71.0%)
Other food allergy n (%)	67 (61.5%)	17 (54.8%)

IgE: immunoglobulin E; kUA/L: kilounits of allergen-specific IgE per litre; Q: quartile.
Source: Vickery et al., 2020[64]; ARC004 clinical study report[65]

Protocol changes

A number of major changes to the protocol affecting trial methods and outcomes occurred after [redacted].[65] The full list of major protocol amendments is presented in Table 66 in Appendix L. The key changes were:

Table 11: **Key protocol changes in the ARC004 (PALISADE follow-on) study**

Protocol change	Rationale
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

Source: ARC004 Clinical Study Report[65]; Aimmune Therapeutics data on file.

2.3.4 ARTEMIS (ARC010)

Trial design

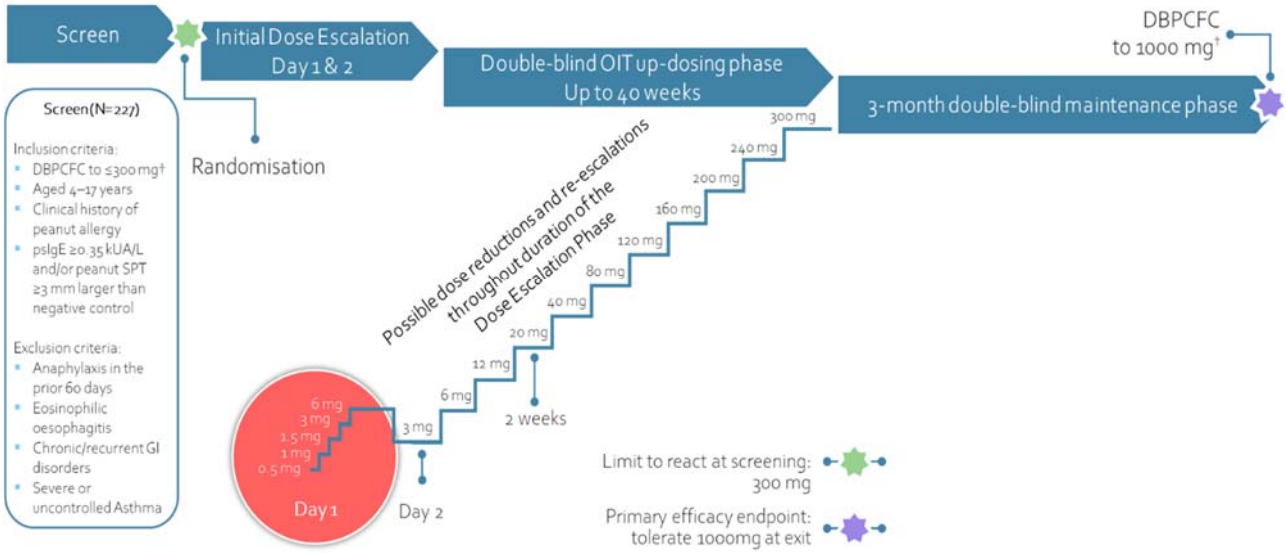
ARTEMIS was a phase 3, international, randomised (3:1), double-blind, placebo-controlled study to evaluate the efficacy and safety of Palforzia OIT for the treatment of peanut allergy in children and adolescents in Europe. The trial design is similar to PALISADE[37] but with some key differences. Trial design details are presented in Table 5 and Figure 12Figure 12.

The study planned to enrol 160 peanut-allergic participants aged 4 to 17 years. Participants were required to have allergic dose-limiting symptoms at a challenge dose of 300 mg or less of peanut protein in a DBPCFC at screening. During the challenges, increasing amounts of peanut protein (not Palforzia) or placebo (oat flour, not study placebo) were mixed in a vehicle food and administered at 20- to 30-minute intervals (Table 6).[37]

Participants were randomised in a 3:1 ratio to either the Palforzia or placebo arms. Randomisation was performed in blocks of eight by a proprietary interactive online response system using a computerised random number generator.[37]

The trial design schema is presented in Figure 12.

Figure 12: ARTEMIS (ARC010) trial design schema



Entry and exit DBPCFCs were conducted by a blinded assessor. * Prophylactic medication use was not allowed during the trial; † Dose of peanut protein
DBPCFC: double-blind, placebo-controlled food challenge; GI: gastrointestinal; OIT: oral immunotherapy; psIgE, serum peanut-specific immunoglobulin E; SPT: skin prick test.
Source: Adapted from Hourihane et al., 2020[37]

Eligibility criteria

ARTEMIS enrolled peanut-allergic participants aged 4 to 17 years. Detailed eligibility criteria are presented in Table 12.

Table 12: ARTEMIS (ARC010) eligibility criteria

Study (acronym)	ARC010 (ARTEMIS)
Inclusion criteria	• Age 4 through 17 years (inclusive) • Clinical history of allergy to peanuts or peanut-containing foods • Serum IgE to peanut ≥ 0.35 kUA/L (determined by a commercial test system, ImmunoCAP, [formerly UniCAP], within the past 12 months) and/or a skin prick test to peanut mean wheal diameter ≥ 3 mm compared with control • Experienced dose-limiting symptoms after consuming a single dose of peanut protein ≤ 300 mg at the screening DBPCFC • Written informed consent from participants or parent/legal guardian for all participants (or both parents when required by local authorities) • Written assent from minor participants as appropriate (in accordance with local regulatory requirements)

	• Use of effective birth control by female participants of childbearing potential
Exclusion criteria	• History of haemodynamically significant cardiovascular disease, including uncontrolled or inadequately controlled hypertension • History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of the screening DBPCFC • History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that was, or was at significant risk of becoming, unstable or required a change in chronic therapeutic regimen, including autoimmune diseases and malignancies (including malignancies occurring in the 5 years before screening) • History of eosinophilic oesophagitis, other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease, symptoms of dysphagia (e.g., difficulty swallowing, food getting stuck), or recurrent gastrointestinal symptoms of undiagnosed etiology • Current participation in another interventional study and/or participation in another interventional clinical study within 30 days or 5 half-lives of the study product, whichever is longer, prior to randomisation • Participated in or received active treatment in any previous clinical study of Palforzia. • Currently receiving or received active treatment in the 5 years prior to screening any type of peanut or any other food immunotherapy clinical study (including subcutaneous, sublingual, oral, or epicutaneous) • In build-up phase of immunotherapy to another allergen (i.e., had not reached maintenance) • Severe asthma (2007 NHLBI criteria steps 5 or 6). • Mild or moderate asthma (2007 NHLBI criteria steps 1-4), if uncontrolled or difficult to control • History of high-dose corticosteroid use (e.g., 1-2 mg/kg prednisone or the equivalent for > 3 days) • Inability to discontinue antihistamines 5 half-lives of the medication before the initial day of escalation, skin prick testing, or DBPCFC • Lack of an available palatable vehicle food to which the subject is not allergic • Use of any therapeutic antibody (e.g., omalizumab, mepolizumab, reslizumab, dupilumab) or any other immunomodulatory therapy excluding aeroallergen or venom immunotherapy, or corticosteroids within the past 6 months • Use of beta blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or tricyclic antidepressants. • Pregnant or lactating • Resided in the same place as another subject in the study or any peanut OIT study • Developed dose-limiting symptoms to the placebo part of the screening DBPCFC • History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, hereditary or idiopathic angioedema, and chronic spontaneous urticaria or other physician-diagnosed physical urticaria syndrome

	• Allergy to oat • Hypersensitivity to adrenaline and any of the excipients of the product • Any other condition that precluded participation for safety reasons, in the opinion of the investigator • Inability to follow protocol requirements • Patient was in any relationship or dependency with the sponsor and/or investigator • Subject had a history of alcohol, medication, or drug abuse.

DBPCFC: double-blind placebo-controlled food challenge; NHLBI: National Heart, Lung, and Blood Institute; OIT: oral immunotherapy
Source: Hourihane et al., 2020[37]

Settings and locations where data were collected

Details of the settings of data collection are presented in Table 5.

Briefly, ARTEMIS was conducted at 18 sites in 7 countries in Europe: Ireland, France, Germany, Italy, Spain, Sweden and the United Kingdom.[37]

As with PALISADE, supervised administration of the first dose at each new dose level and the first dose of each kit issued during maintenance (every 4 weeks) regimen occurred in a secondary/tertiary care setting. Daily dosing continued at home.[37]

Trial drugs and concomitant medication

Overall, 175 participants aged 4 to 17 years were enrolled in ARTEMIS. Of these, 132 were randomised into the Palforzia arm and 43 were randomised into the placebo arm.[37]

Trial treatment regimens and concomitant medication are detailed in Table 5. Briefly, the trial was undertaken in three phases:

- **Dose-escalation phase** (2 days): participants received escalating doses of Palforzia (0.5 to 6 mg) or placebo at the study site on day 1 and a 3 mg dose on day 2, followed by observation for at least 90 minutes.[37] Day 2 represents the first up-dosing visit.
- **Up-dosing phase** (20-40 weeks): participants received escalating doses of Palforzia (3 to 300 mg/day) or placebo at 2-week intervals.[37]
- **Maintenance phase** (12 weeks): participants received 300 mg/day of Palforzia or placebo.[37]

The total duration of treatment was approximately 9 months.[37]

Outcomes used in the economic model or specified in the scope, including the primary outcome

The outcomes of the ARTEMIS study were pre-specified. In participants aged 4 to 17 years with peanut allergy, the outcomes were:

Primary outcome

- Peanut allergy desensitisation: the proportion of participants who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulative) without dose-limiting symptoms.[37]

Key secondary outcomes

- Proportion of participants who tolerated single doses of 600 mg (1043 mg cumulative dose) and 300 mg (443 mg cumulative dose) peanut protein at the exit food challenge[37]

Other outcomes

- Food allergy-related quality of life assessments by use of FAQLQ and FAIM instruments[37]
    - Frequency and severity of symptoms after accidental exposure to peanut (referred to as “Accidental exposure to peanut requiring treatment with and without adrenaline”).[37] Since accidental exposures are uncommon, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate endpoint.

Please see Table 5 for details on the included outcomes.

Participant baseline characteristics

The baseline characteristics of participants in the ARTEMIS study were well balanced between the trial arms and typical of a population with atopic peanut allergy (Table 13).[37] Detailed participant characteristics are presented in Table 67 in Appendix L.

Table 13: Key characteristics of participants aged 4 to 17 years across treatment groups in the ARTEMIS (ARC010) study

	Palforzia N=132	Placebo N=43	Total N=175
Age, years			

Median	[redacted]	[redacted]	[redacted]
4–11 years, n (%)	97 (73.5%)	30 (69.8%)	127 (72.6%)
12–17 years, n (%)	35 (26.5%)	13 (30.2%)	48 (27.4%)
Sex			
Male, n (%)	68 (51.5%)	27 (62.8%)	95 (54.3%)
Geographic region			
United Kingdom n (%)	[redacted]	[redacted]	[redacted]
Germany n (%)	[redacted]	[redacted]	[redacted]
Spain n (%)	[redacted]	[redacted]	[redacted]
Ireland n (%)	[redacted]	[redacted]	[redacted]
France n (%)	[redacted]	[redacted]	[redacted]
Sweden n (%)	[redacted]	[redacted]	[redacted]
Italy n (%)	[redacted]	[redacted]	[redacted]
Peanut-specific IgE (kUA/L)			
Median (Q1, Q3)	43.50 (5.20, 147.00)	69.70 (20.70, 103.00)	[redacted]
Prick test mean wheal diameter (mm)			
Median (Q1, Q3)	9.50 (7.50, 12.25)	9.75 (8.00, 12.50)	9.50 (8.00, 12.50)
Non-peanut allergy history			
Allergic rhinitis n (%)	63 (47.7%)	16 (37.2%)	79 (45.1%)
Asthma n (%)	56 (42.4%)	14 (32.6%)	70 (40%)
Atopic dermatitis n (%)	78 (59.1%)	22 (51.2%)	100 (57.1%)
Other food allergy n (%)	81 (61.4%)	21 (48.8%)	102 (58.3%)

IgE: immunoglobulin E; kUA/: kilounits of allergen-specific IgE per litre; Q: quartile.
Source: Hourihane et al., 2020[37]; ARC010 Clinical study report[76]

Protocol changes

A number of major changes to the protocol affecting trial methods and outcomes occurred after trial commencement.[76] The full list of major protocol amendments is presented in Table 68 in Appendix L. The key changes were:

Table 14: **Key protocol changes in the ARC010 (ARTEMIS) study**

Protocol change	Rationale
Protocol Amendment 1, Version 2.0 (Global) – 16Jan2017	
Modified inclusion criterion 3 to remove the upper limit of serum IgE to peanut and include participants with serum IgE to peanut of at least 0.35 kUA/L.	[redacted]

Source: ARC010 Clinical Study Report[76]; Aimmune Therapeutics data on file.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details about the statistical methodology of the identified RCTs is presented in Table 15. Participant flow diagrams for the clinical trials are available in Appendix D1.3.

Table 15: Summary of statistical analyses

Study (acronym)	ARC003 (PALISADE)[38]	ARC004 (PALISADE follow-on)[64,65]	ARC010 (ARTEMIS)[37]
Hypothesis objective	To detect a between-group difference in desensitisation response rates among participants aged 4 to 17 years. Null hypothesis: the absolute difference in response rates (active drug group minus placebo group) would be equal to 0 at the 0.05 significance level. The primary endpoint will have been met if the lower bound of the corresponding 95% confidence interval (CI) is >0.	No specific hypothesis testing or comparisons between treatment groups were performed.	To detect a between-group difference in desensitisation response rates Null hypothesis: the absolute difference in response rates (active drug group minus placebo group) would be equal to 0 at the 0.05 significance level. The primary endpoint will have been met if the lower bound of the corresponding 95% confidence interval (CI) is >0.
Analysis population	• The intention-to-treat (ITT) population of participants aged 4 to 17 years was used as the primary analysis population for all efficacy endpoints • The ITT population included all participants aged 4 to 17 years randomly assigned to treatment who received ≥1 dose of study product • Sensitivity analyses and supportive analyses of the primary efficacy endpoint, key secondary endpoints and other secondary endpoints were performed using the completer population • The completer population included all participants in the ITT population who completed treatment and had an evaluable exit DBPCFC (completion of at least the peanut part of the food challenge).	• The safety population was used for the primary endpoint analyses [redacted] • The safety population included all participants who received at least 1 dose of Palforzia during ARC004 [redacted] [redacted] • The completer population included all participants in the safety population who had at least 1 evaluable DBPCFC ([redacted]) • [redacted]	• The ITT population was used as the primary analysis population for all efficacy endpoints. • The ITT population included all participants randomly assigned to treatment who received ≥1 dose of study product • Sensitivity analyses and supportive analyses of the primary efficacy endpoint, key secondary endpoints and other secondary endpoints were performed using the completer population. • The completer population included all participants in the ITT population who completed treatment and had an evaluable exit DBPCFC • Sensitivity analyses of the primary and all secondary efficacy endpoints were to be performed using the per protocol

	• Analyses of the primary and all secondary efficacy endpoints were to be performed using the per protocol population if it differed from the completer population by >5% in either treatment group • The per protocol population was a subset of the completer population, limited to participants without major protocol deviations that could influence the desensitisation response • Sensitivity analyses of selected endpoints could be performed if the per protocol population differed from the completer population by ≤5% in both treatment groups	• [redacted] *Note: since ARC004 explored different dosing regimens of* Palforzia*, only the cohorts that remained on daily dosing in ARC004 (Cohorts 1 and 3A), per the labelled indication of* Palforzia*, were used to populate the economic model.*	population if it differed from the completer population by >5% in either treatment group • The per protocol population was a subset of the completer population, limited to participants without major protocol deviations that could influence the desensitisation response • Sensitivity analyses of selected endpoints could be performed if the per protocol population differed from the completer population by ≤5% in both treatment groups
Statistical analysis	• All statistical tests were two-sided with a 0.05 significance level • CIs were calculated at the 95% level, type I error rate of 0.05 • For the primary analysis of the primary efficacy endpoint, the number and percent of participants with a desensitisation response were reported by treatment group • The desensitisation response rate and its 95% CI were calculated for each treatment group with Wilson (score) confidence limits for the binomial proportion. The 95% CI for the treatment difference (Palforzia desensitisation rate minus placebo desensitisation rate) was based on Farrington-Manning CI for the difference in binomial proportions.	• Data were summarised using descriptive statistics by group/cohort • [redacted]	As per PALISADE, with the following exception: • The desensitisation response rate and its 95% CI were calculated for each treatment group using the exact Clopper Pearson method. The 95% CI was based on the exact unconditional confidence limits using the score statistic. • Desensitisation response rates were compared between treatment groups using Fisher's exact test

	• The number and percent of participants at each dose level for highest tolerated dose at the exit DBPCFC were summarised by treatment group. • If the primary efficacy endpoint analysis was significant at the 0.05 level, the key secondary efficacy endpoints were evaluated in the following hierarchical order: 1. Peanut allergy desensitisation at 600 mg (1043 mg cumulative): The proportion of participants aged 4 to 17 years who tolerated a single highest dose of ≥600 mg of peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC 2. Peanut allergy desensitisation at 300 mg (443 mg cumulative): The proportion of participants aged 4 to 17 years who tolerated a single highest dose of ≥300 mg of peanut protein (443 mg cumulative) with no more than mild symptoms at the exit DBPCFC 3. The maximum symptom severity in participants aged 4 to 17 years that occurred at any challenge dose of peanut protein during the exit DBPCFC • If all the key secondary efficacy outcomes are met, statistical testing of the other secondary efficacy endpoints were to be evaluated in the following hierarchical order:		

	1. Maximum dose achieved with no or mild symptoms at exit DBPCFC 2. Change from baseline in maximum tolerated dose (MTD) of peanut protein at DBPCFC 3. Use of adrenaline as a rescue medication at exit DBPCFC and comparison to its use at screening DBPCFC 4. Changes in peanut-specific serum IgE and IgG4 levels 5. Changes in peanut skin prick test (SPT) mean wheal diameters 6. Quality of life assessment using the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire • Once a non-significant result was obtained during the hierarchical testing, all subsequent key secondary endpoint analyses were to be considered exploratory.		
Sample size, power calculation	In total, 555 participants aged 4 to 55 years were randomised. • Participants aged 4 to 17 years (primary study population): 499 participants	In total, 358 participants aged 4 to 17 years continued into the ARC004 study Accrual of 80% of the total ARC003 sample into ARC004 would provide an 80% probability of observing at least 1 AE with a background rate of 4 per 1000 participants. There was no prospective power calculation for efficacy.	In total, 175 participants aged 4 to 17 years were randomised (132 in Palforzia arm, 43 in placebo arm). Assuming a maximum placebo response rate of 15% at a single dose of 1000 mg (2043 mg cumulative) of peanut protein, a sample size of 120 Palforzia-treated participants and 40 placebo-treated participants provided at least 90% power to detect a Palforzia response rate of at least

	randomised (372 in Palforzia arm, 125 in placebo arm). • Participants aged 18 to 55 years: 56 participants randomised (42 in Palforzia arm, 14 in placebo arm) Assuming a placebo response rate of 15% at a single dose of 1000 mg (2043 mg cumulative) of peanut protein, a sample size of 495 participants aged 4 to 17 years provided at least 93% power to detect a Palforzia response rate of at least 30% at a single dose of 1000 mg peanut protein at the exit DBPCFC.		43% at a single dose of 1000 mg peanut protein at the exit DBPCFC.
Data management, patient withdrawals	• For primary and secondary endpoints involving desensitisation rates, participants who discontinue prior to the exit DBPCFC will be considered non-responders • For key secondary endpoint of maximum severity of symptoms, if a subject discontinues prior to the exit DBPCFC, the maximum severity of symptoms during the exit DBPCFC will be imputed using the maximum severity of symptoms during the screening DBPCFC • 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 participants with missing data (i.e., no exit DBPCFC), placebo-treated participants were to be considered responders, and Palforzia-		• For primary and secondary endpoints involving desensitisation rates, participants who discontinue prior to the exit DBPCFC will be considered treatment failures • Sensitivity analyses were conducted using a worst-case approach to missing data imputation to determine the impact of missing data on the robustness of the study results. For the worst-case imputation analysis, placebo-treated participants with missing data for the exit DBPCFC were considered responders (i.e., as successfully passing the food challenge) and Palforzia-treated participants with missing data for the exit DBPCFC were considered non-responders (i.e., as not passing the food challenge).

	treated participants were to be considered non-responders. Analytical methods were the same as those used for the primary analysis. If the primary analysis of the primary efficacy endpoint showed a statistically significant treatment effect, a tipping point analysis was to be conducted to identify the point at which the number placebo-treated participants with missing data imputed as responders made the treatment effect non-significant.		

AE: adverse event; CI: confidence interval; DBPCFC: double-blind placebo-controlled food challenge; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy-Related Quality of Life Questionnaire; ITT: intention-to-treat; mITT: modified intention-to-treat; MTD: maximum tolerated dose; SPT: skin prick test

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 16: Quality assessment results for parallel group RCTs*

Trial number (acronym)	ARC003 (PALISADE)	ARC004 (PALISADE follow-on)	ARC010 (ARTEMIS)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	N/A	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	N/A	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes The ITT analysis was appropriate. Appropriate measures were used to account for missing data.	No	Yes The ITT analysis was appropriate. Appropriate measures were used to account for missing data.

ITT: intention-to-treat; N/A: not applicable; RCT: randomised controlled trial.
*Quality assessment of studies is based on information provided in the Clinical Study Reports rather than the publication.

Detailed quality assessment of RCTs is available in Appendix D1.4.

B.2.6 Clinical effectiveness results of the relevant trials

By increasing the amount of peanut protein tolerated, Palforzia aims to reduce the risk of anaphylactic reactions if a peanut-allergic patient is exposed to peanuts. In the clinical trials, Palforzia provides protection to 600 mg and 1000 mg of peanut protein (clinical trial endpoints), which is approximately five- to eight-fold the amount of peanut protein encountered in real life that triggers reactions (125 mg median; corresponding to half a peanut kernel).[27] If a patient is able to tolerate 600 mg or even 1000 mg of peanut protein while on treatment with Palforzia, this patient

will have additional protection from reactions to accidental exposure to peanut, even if cofactors exist. Therefore, the endpoints studied in Palforzia's clinical trials are clinically meaningful and relevant to both the patient and their caregivers (see section B.2.3.1 for an overview of the DBPCFC endpoints).

2.6.1 PALISADE (ARC003)

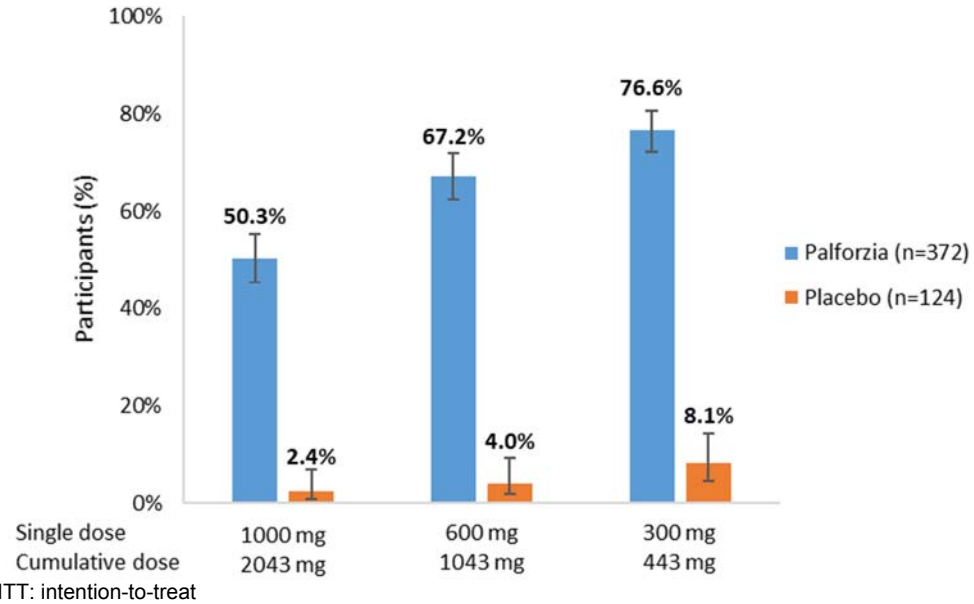
Primary efficacy endpoint

The primary efficacy endpoint—the proportion of participants aged 4 to 17 years who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulative) without dose-limiting symptoms—was met (Figure 13).[66]

In the ITT population, the desensitisation response rate was 50.3% in the Palforzia arm (n=372) compared with 2.4% in the placebo arm (n=124). The treatment difference (Palforzia-placebo) was 47.8% (95% CI: 38.0, 57.7; p<0.0001).[38,66]

[redacted] (see Table 64 in Appendix L for the summary of sensitivity analyses to the primary efficacy endpoint).[39]

Figure 13: PALISADE (ARC003) peanut desensitisation rates in participants aged 4 to 17 years (ITT population)



ITT: intention-to-treat
Error bars represent 95% confidence intervals
Source: Adapted from Vickery et al. 2018[38], Palforzia EPAR[66]

Secondary endpoints

Key secondary endpoints

All key secondary endpoints were met in hierarchical order. Among participants aged 4 to 17 years in the ITT population:

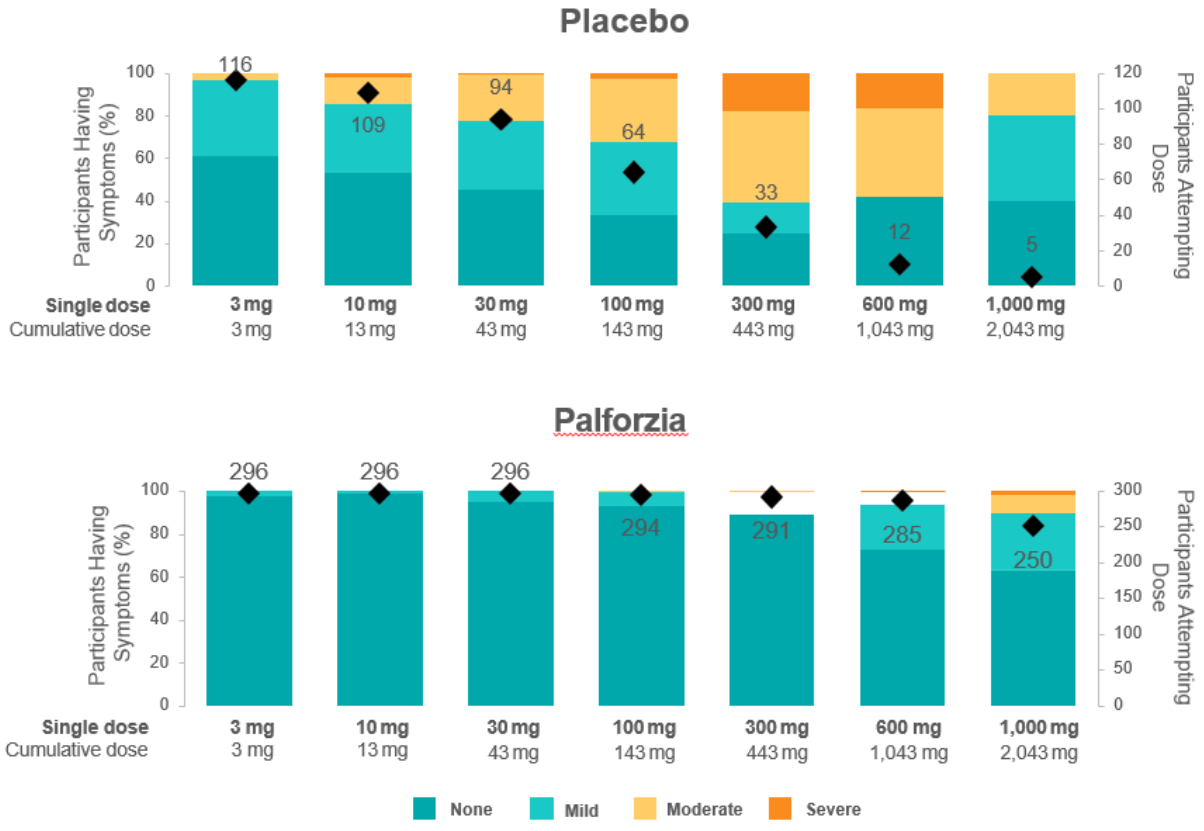
- *The proportion of participants who tolerated at least 600 mg peanut protein (1043 mg cumulative) without dose-limiting symptoms* was 67.2% (95% CI: 62.3, 71.8) for participants who received Palforzia (n=372) compared with 4.0% (95% CI: 1.7, 9.1) for participants who received placebo (n=124) (Figure 13). The treatment difference (Palforzia-placebo) was 63.2% (95% CI: 53.0, 73.3; p<0.0001).[38,66]
- *The proportion of participants who tolerated at least 300 mg peanut protein (443 mg cumulative) without dose-limiting symptoms* was 76.6% (95% CI: 72.1, 80.6) for participants in the Palforzia arm (n=372) compared with 8.1% (95% CI: 4.4, 14.2) for participants in the placebo arm (n=124) (Figure 13). The treatment difference (Palforzia-placebo) was 68.5% (95% CI: 58.6, 78.5; p<0.0001).[38,66]

Other endpoints

- *Frequency and severity of symptoms after accidental exposure to peanut (Accidental exposure to peanut requiring treatment with and without adrenaline)*: During the approximately 6-month maintenance period, [redacted] of participants in the Palforzia arm and [redacted] participants in the placebo arm had accidental exposure to peanut. Only [redacted] of Palforzia-treated participants experienced an adverse event (AE) following accidental peanut exposure that required treatment compared to [redacted] in the placebo-treated participants. [redacted] accidental peanut exposure in the Palforzia arm required adrenaline use compared to [redacted] in the placebo arm.[77] Since accidental exposures to peanut are uncommon, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate (Figure 14).

Results show that, when participants on Palforzia were exposed to peanut, the majority was able to ingest large amount of peanut with no symptoms at all, or with mild symptoms. This is reflected by the fact that most patients continued ingesting the sequential doses of peanut (please see diamonds in Figure 14). In contrast, when the placebo participants were exposed to peanut, not only did they react to small amounts of peanut, but they did so with an increased severity of reaction. Therefore, treatment with Palforzia reduced the severity of reactions when peanut exposure occurred, even when the amount of peanut was considerably high.

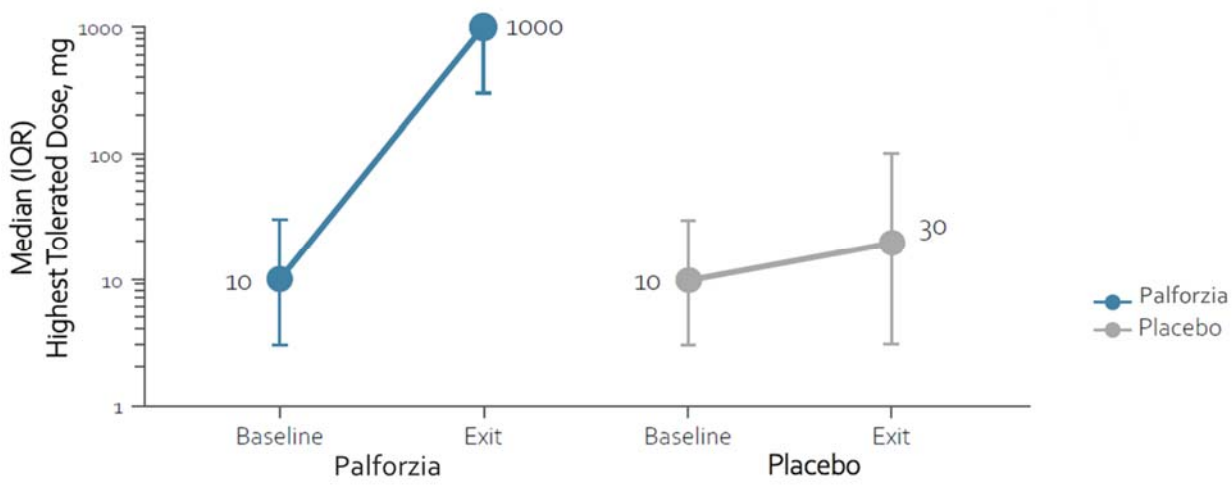
Figure 14: PALISADE (ARC003) maximum severity of symptoms occurring during each dose of the exit DBPCFC with peanut among participants aged 4 to 17 years (completer population)



DBPCFC: double-blind, placebo-controlled food challenge.
Bars are measured on the primary Y-axis and diamonds are measured on the secondary Y-axis.
Source: Adapted from Vickery et al. 2018[Error! Reference source not found.]

- *Highest tolerated dose at Entry and Exit DBPCFC:* Palforzia-treated participants experienced a 100-fold increase in highest tolerated dose from baseline to study exit (Figure 15). The corresponding increase in placebo-treated participants was 3-fold.

Figure 15: PALISADE (ARC003) highest tolerated dose at Entry and Exit DBPCFC in participants aged 4 to 17 years (ITT population)



DBPCFC: double-blind, placebo-controlled food challenge; IQR: interquartile range; ITT: intention-to-treat
Source: Jones et al, 2018[78]

- *Improvement in quality of life as measured by FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales*: See results in Section B.2.6.4 and discussion in Section B.2.13.

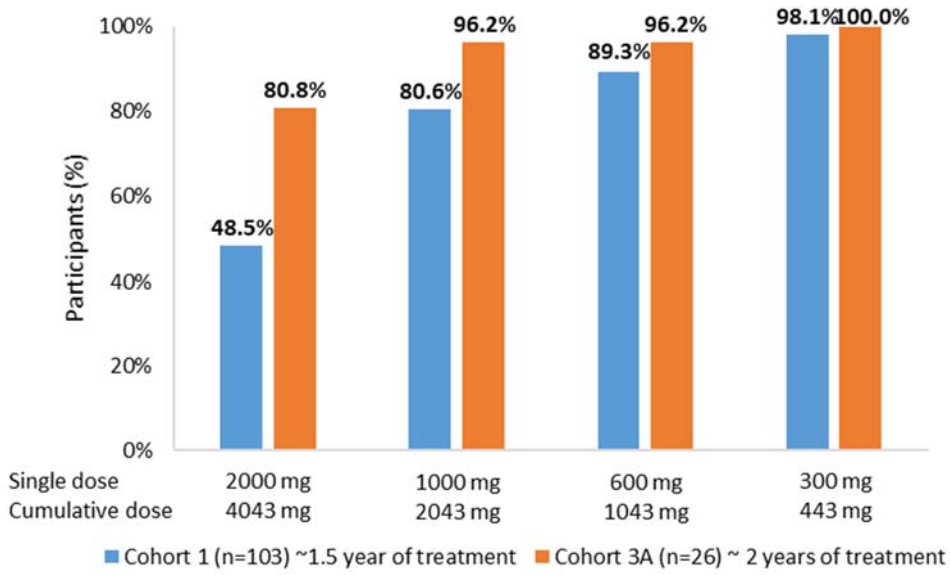
2.6.2 PALISADE follow-on (ARC004)

Efficacy analyses were secondary endpoints in ARC004.[66] After an additional 28 weeks (Cohort 1) or 56 weeks (Cohort 3A) of Palforzia 300 mg/day treatment, participants received a total of approximately 13 and 20 months of Palforzia daily maintenance treatment, respectively.[64] Among participants aged 4 to 17 years who received 300 mg Palforzia daily as maintenance treatment:

- *The proportion of participants who tolerated at least 2000 mg peanut protein (4043 mg cumulative) without dose-limiting symptoms* was 48.5% (95% CI: 38.6, 58.6) for participants in Cohort 1 (n=103) and 80.8% (95% CI: 60.6, 93.4) for participants in Cohort 3A (n=26) (Figure 16).[66]

- *The proportion of participants who tolerated at least 1000 mg peanut protein (2043 mg cumulative) without dose-limiting symptoms* was 80.6% (95% CI: 71.6, 87.7) for participants in Cohort 1 (n=103) and 96.2% (95% CI: 80.4, 99.9) for participants in Cohort 3A (n=26) (Figure 16).[66]
- *The proportion of participants who tolerated at least 600 mg peanut protein (1043 mg cumulative) without dose-limiting symptoms* was 89.3% (95% CI: 81.7, 94.5) for participants in Cohort 1 (n=103) and 96.2% (95% CI: 80.4, 99.9) for participants in Cohort 3A (n=26) (Figure 16).[66]
- *The proportion of participants who tolerated at least 300 mg peanut protein (443 mg cumulative) without dose-limiting symptoms* was 98.1% (95% CI: 93.2, 99.8) for participants in Cohort 1 (n=103) and 100% (95% CI: 86.8, 100) for participants in Cohort 3A (n=26) (Figure 16).[66]

Figure 16: Desensitisation rates based on the tolerated dose at the exit DBPCFC (ARC004 PALISADE follow-on; completer population; N=129)



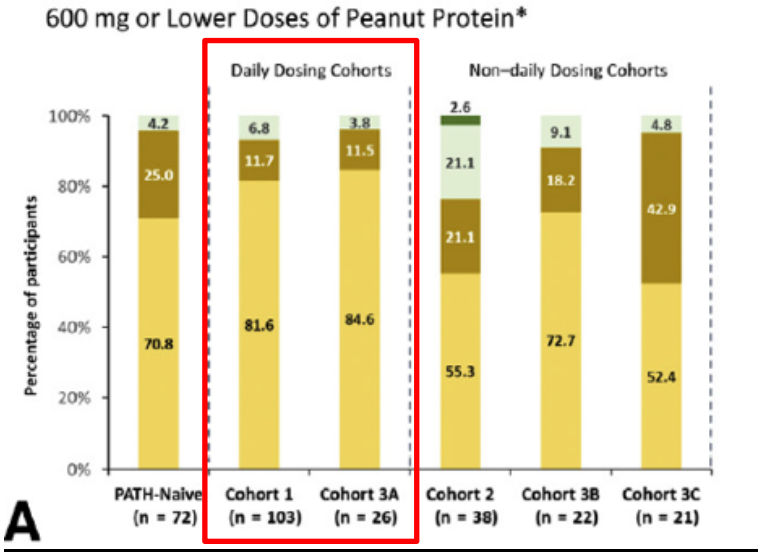
Source: Adapted from Vickery et al., 2020[64]

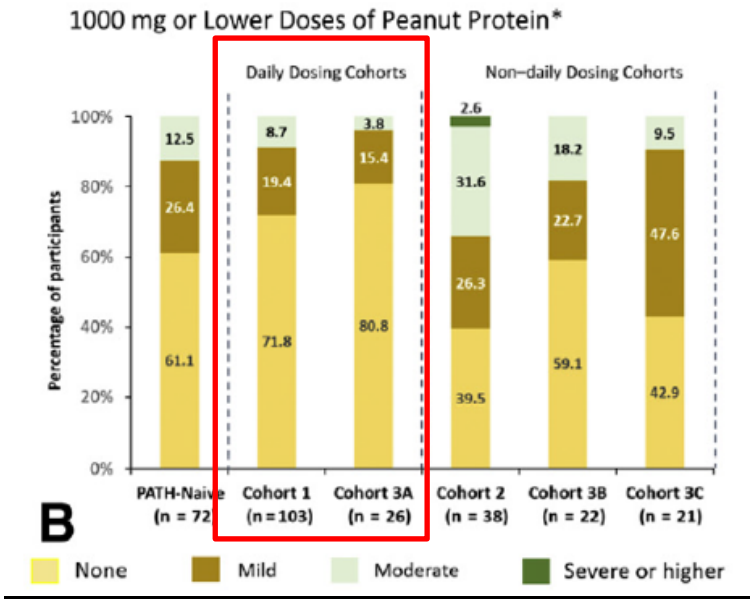
- *Frequency and severity of symptoms after accidental exposure to peanut (Accidental exposure to peanut requiring treatment with and without adrenaline):* Over the course of the study, [redacted] in Cohort 1 and [redacted] in Cohort 3A experienced accidental exposure to peanut.[65] [redacted] in Cohort 1 and [redacted] in Cohort 3A required treatment for accidental peanut exposure; [redacted]

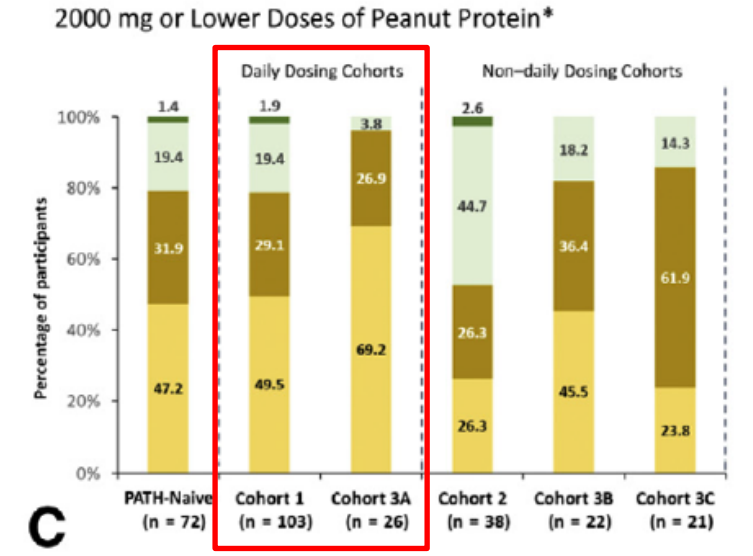
[redacted] experienced accidental peanut exposure requiring adrenaline use. [Aimmune Therapeutics data on file].

Since accidental exposures are very rare, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate (Figure 17). When focussing on Cohort 1 and 3A in Figure 17, the majority of the participants did not present any symptom when exposed to considerable amounts of peanut, such as 600 or 1000 mg of peanut protein. Similarly, most of the participants treated with Palforzia for longer (cohort 3A) did not react when exposed to even the highest amount of peanut (2000 mg of peanut protein).

Figure 17: Maximum severity of symptoms occurring at peanut challenge doses of 600 mg or lower (A), 1000 mg or lower (B) and 2000 mg or lower (C) during the exit DBPCFC (completer population) in ARC004







DBPCFC: double-blind, placebo-controlled food challenge; PATH: peanut (*Arachis hypogaea*) allergy powder-dnfp.
Daily dosing cohorts received 300 mg/day Palforzia for 28 weeks (Cohort 1) or 56 weeks (Cohort 3A). See Table 5 and Figure 11 for the full description of dosing regimens.
Source: Vickery et al., 2020[Error! Reference source not found.]

- *Improvement in quality of life as measured by FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales*: See results in Section B.2.6.4 and discussion in Section B.2.13.

2.6.3 ARTEMIS (ARC010)

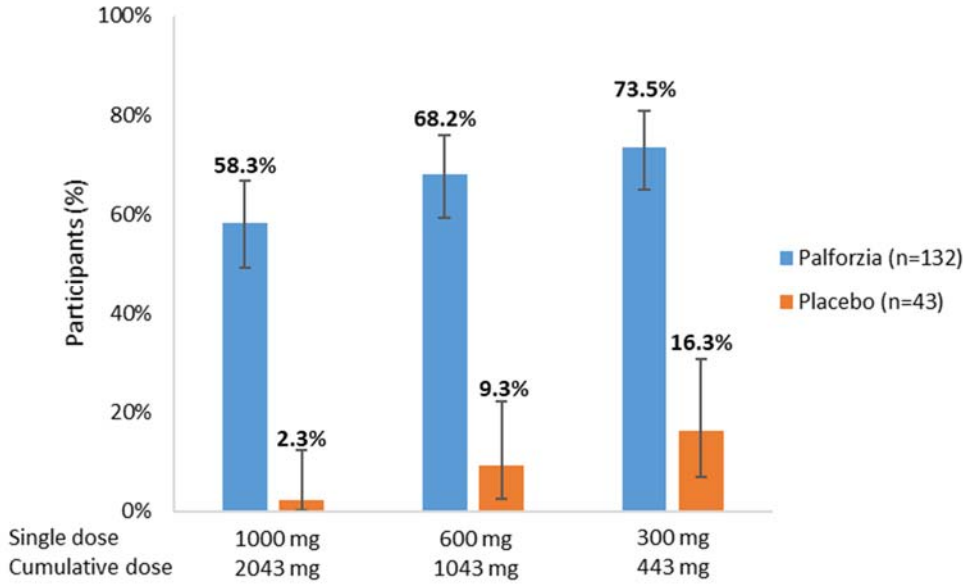
Primary efficacy endpoint

The primary efficacy endpoint–the proportion of participants who tolerated a single dose of at least 1000 mg peanut protein [cumulative dose 2043 mg] with no more than mild symptoms at the exit DBPCFC–was met (Figure 18).[37]

In the ITT population, the desensitisation response rate was 58.3% in the Palforzia arm (n=132) compared with 2.3% in the placebo arm (n=43). The treatment difference (Palforzia-placebo) was 56.0% (95% CI: 44.1, 65.2; p<0.0001).[37]

All sensitivity analyses were [redacted] (see Table 69 in Appendix L).[76]

Figure 18: ARTEMIS (ARC010) peanut desensitisation rates (ITT population)



Source: Adapted from Hourihane et al., 2020[37]; Palforzia EPAR[66]

Secondary endpoints

Key secondary endpoints

All key secondary endpoints were met in hierarchical order.[37] Among participants in the ITT population:

- *The proportion of participants who tolerated at least 600 mg peanut protein (1043 mg cumulative) without dose-limiting symptoms* was 68.2% (95% CI: 59.5, 76.0) for participants who received Palforzia (n=132) compared with 9.3% (95% CI: 2.6, 22.1) for participants who received placebo (n=43) (Figure 18). The treatment difference (Palforzia-placebo) was 58.9% (95% CI: 44.2, 69.3; p<0.0001).[37,66]
- *The proportion of participants who tolerated at least 300 mg peanut protein (443 mg cumulative) without dose-limiting symptoms* was 73.5% (95% CI: 65.1, 80.8) for participants who received Palforzia (n=132) compared with 16.3% (95% CI: 6.8, 30.7) for participants who received placebo (n=43) (Figure 18). The treatment difference (Palforzia-placebo) was 57.2% (95% CI: 41.2, 69.1; p<0.0001).[37,66]

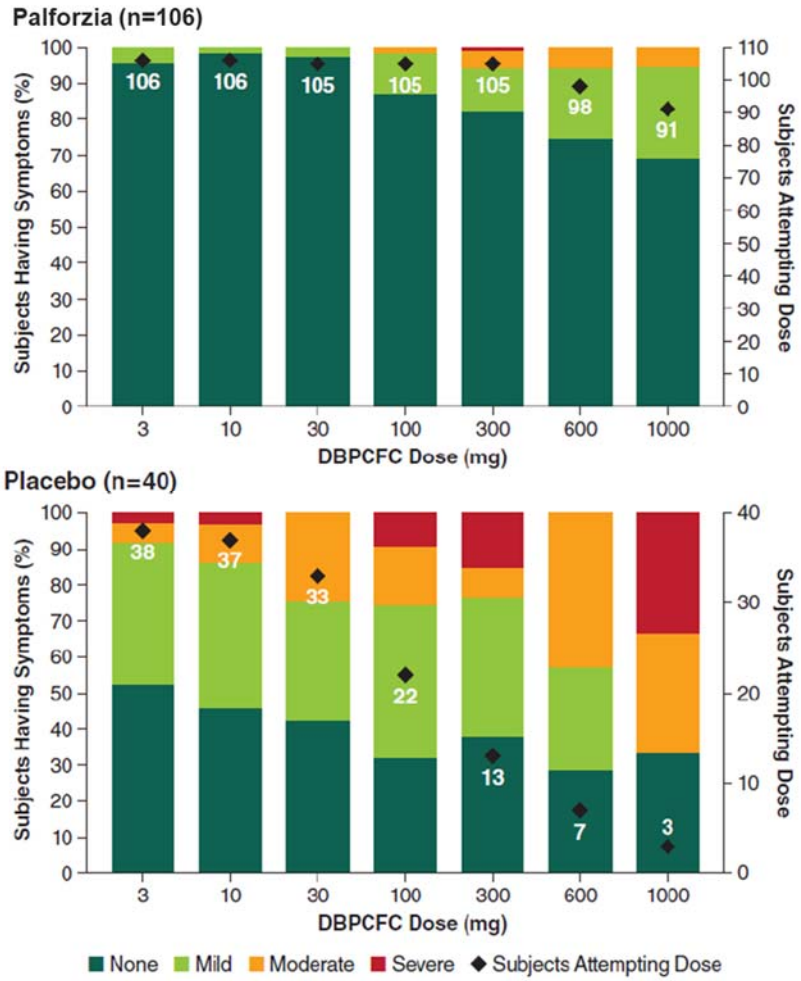
Other endpoints

- *Frequency and severity of symptoms after accidental exposure to peanut (Accidental exposure to peanut requiring treatment with and without*

adrenaline): During the maintenance phase of ARTEMIS, [redacted] in the Palforzia arm experienced accidental exposure to peanut compared to [redacted] in the placebo arm. [redacted] required treatment or adrenaline after accidental peanut exposure.[77] Since accidental exposures are uncommon, the severity of symptoms occurring at the exit DBPCFC is used as a surrogate (Figure 19).

These results demonstrate that, when participants treated with Palforzia were exposed to peanut, they experienced less severe symptoms (mostly no symptoms at all, or only mild symptoms), even if the amount of peanut ingested was considerably high. In comparison, the placebo participants could suffer moderate and severe reactions when exposed to small amounts of peanut.

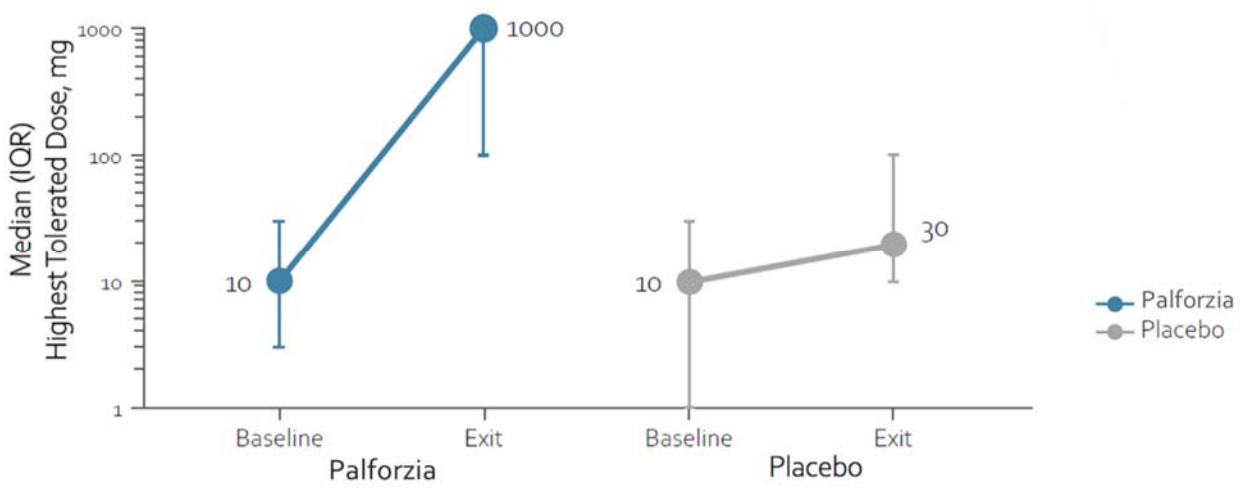
Figure 19: Maximum severity of symptoms occurring during each dose of the exit DBPCFC among participants aged 4 to 17 years (completer population)



DBPCFC: double-blind, placebo-controlled food challenge
Bars are measured on the primary Y-axis and points are measured on the secondary Y-axis.
Source: Hourihane et al. 2020 Error! Reference source not found.

- *Highest tolerated dose at Entry and Exit DBPCFC:* Palforzia-treated participants experienced a 100-fold increase in highest tolerated dose from baseline to study exit (Figure 20). The corresponding increase in placebo-treated participants was 3-fold.

Figure 20: ARTEMIS (ARC010) highest tolerated dose at Entry and Exit DBPCFC (ITT population)



DBPCFC: double-blind, placebo-controlled food challenge; IQR: interquartile range; ITT: intention-to-treat
Source: Hourihane et al. 2020 [Error! Reference source not found.]; ARC010 Clinical study report[76]

- Improvement in quality of life as measured by FAQLQ (Food Allergy-Related Quality of Life Questionnaire) and FAIM (Food Allergy Independent Measure) scales: See results in Section B.2.6.4 and discussion in Section B.2.13

2.6.4 Improvement in participant disease-specific health-related quality of life (HRQoL) as measured by the Food Allergy-Related Quality of Life Questionnaire (FAQLQ) and the Food Allergy Independent Measure (FAIM) in the PALISADE, ARC004 follow-on and ARTEMIS trials

Participant disease-specific health-related quality of life (HRQoL) was measured during the PALISADE, ARC004 and ARTEMIS trials using age-specific versions of the FAQLQ, both self- and parent proxy-reported, and supported by the FAIM as a validation measure.

Description of the FAQLQ measures

The FAQLQ is one of the key food allergy-specific HRQoL measures recommended by the European Academy of Allergy and Clinical Immunology (EAACI) guidelines for use in food allergy clinical trials,[79] and was developed by leading food allergy experts in Europe.[80-86] The FAQLQ contains 23–30 items, depending on version, on a 7-point response scale, with unspecified recall period, and includes domains for allergen avoidance and dietary restrictions, emotional impact, risk of accidental exposure, and food allergy-related health.

There are several versions of the FAQLQ, specifically for children aged 8 to 12 years (FAQLQ-CF), teenagers aged 13 to 17 years (FAQLQ-TF), and adult participants (FAQLQ-AF), as well as parent proxy-report questionnaires for children (FAQLQ-PF) and teenagers (FAQLQ-PFT) respectively. It should be noted that there is no version of the FAQLQ that measures the parent's own HRQoL specifically.

The Minimal Important Difference (MID) of the FAQLQ overall is considered by the developers of the measure to be around 0.5, in line with other quality of life questionnaires with a 7-point scale.[87] Note that a reduction in FAQLQ score represents an improvement in HRQoL.

The MID for the FAQLQ-PF version specifically has been found to be around 0.45.[80]

With successful desensitisation treatment, it was hypothesised that the patient and parental perception of HRQoL would improve from baseline, as measured by the age/respondent appropriate version of the FAQLQ.

The different versions of the FAQLQ (combined with the FAIM) are available for reference in Appendix M.

Description of the FAIM measures

The FAIM was developed by clinicians for use in conjunction with the FAQLQ as an independent validation tool,[88] and as a measure of perceived disease severity. Perceived severity (also called perceived seriousness) refers to the negative consequences an individual associates with an event or outcome, i.e. with an adverse reaction in the case of the FAIM. The self-reported versions (FAIM-CF and FAIM-TF) include questions on the participant's perception of their risk of accidental exposure to

a food allergen, having a severe reaction, dying and of being unable to manage a reaction if one occurs (collectively referred to as the “expectation of outcomes” domain), as well as questions on food and the social limitations of their food allergy. The parent proxy-reported FAIM versions (FAIM-PF and FAIM-PFT) only include the “expectation of outcomes” questions. The FAIM-PF asks these questions from both the parent’s and the child’s perspective, whereas the FAIM-PFT only asks them from the parent’s perspective.

Like the FAQLQ, FAIM has a 7-point response scale and unspecified recall period, and reductions in the score indicate improvement.

With successful desensitisation treatment, it was hypothesised that the participant and parental perception of risk and expectation of a poor outcome if accidentally exposed to peanuts would be significantly reduced, resulting in a decrease in FAIM total and “expectation of outcome” domain score, and that this would in turn be accompanied by improvements in HRQoL as measured by the FAQLQ.

PALISADE and ARC004 FAQLQ and FAIM results

In assessing the impact of food allergy immunotherapy on HRQoL it is important to look at the long-term impact once participants and caregivers are aware of and have adjusted to their level of desensitisation to peanut. Blinded studies are known to have a confounding effect on the assessment of quality of life in the area of food allergy. Specifically, participants and caregivers need to know if they are desensitised to peanuts in order to experience reduced anxiety about reactions and an improvement in HRQoL. When blinded to treatment, participants and caregivers are unaware if they are protected from accidental exposures to peanut or not, hence anxiety about reactions and HRQoL would not be expected to improve, unlike in a real-life treatment setting. Furthermore, even after unblinding, immediate HRQoL improvements are not anticipated. The psycho-social aspects of food allergy-related quality of life covered in the FAQLQ such as avoidance behaviours, social impacts, and dietary restrictions are unlikely to change quickly as participants and caregivers need time to adjust to the knowledge of their new health state. For these reasons, FAQLQ and FAIM results from PALISADE and its follow-on study ARC004 are presented and discussed here

together, to provide a longer-term perspective that may also inform ecological validity of the treatment.

FAQLQ and FAIM were assessed in PALISADE at the screening visit before blinding and at the exit DBPCFC visit immediately after study unblinding. Additionally, these measures were assessed at ARC004 exit, after a further 28 weeks of open label maintenance treatment for Cohort 1 and 56 weeks for Cohort 3A.

Participant self-reported and parent proxy-reported FAQLQ and FAIM mean change from baseline results are reported for PALISADE in Table 17 and for its follow-on study ARC004 in Table 18.

In Table 17 it can be seen that [redacted].[39] [redacted]. This result was as expected for the reasons cited above around the effects of study blinding.

It should also be noted that [redacted], whether by self- or parent proxy-report, and regardless of treatment arm.[39]

Table 17: PALISADE FAQLQ and FAIM mean change from baseline in total score in participants aged 4 to17 years (ITT population)

	Palforzia	Placebo
FAQLQ Total Score		
Self-reported, subjects 8–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
LS mean difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Self-reported, subjects 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
LS mean difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Parent proxy-reported, subjects 4–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
LS mean difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	

Parent proxy-reported, subjects 13–17 years		
Mean change from baseline (SD)		
LS mean difference (Palforzia-placebo) [95% CI]		
P-value		
FAIM Total Score		
Self-reported, subjects 8–12 years		
Mean change from baseline (SD)		
LS mean difference (Palforzia-placebo) [95% CI]		
P-value		
Self-reported, subjects 13 –17 years		
Mean change from baseline (SD)		
LS mean difference (Palforzia-placebo) [95% CI]		
P-value		
Parent proxy-reported, subjects 4–12 years		
Mean change from baseline (SD)		
LS mean difference (Palforzia-placebo) [95% CI]		
P-value		
Parent proxy-reported, subjects 13–17 years		
Mean change from baseline (SD)		
LS mean difference (Palforzia-placebo) [95% CI]		
P-value		

ANCOVA: analysis of covariance; CI: confidence interval; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; ITT: intention-to-treat; LS: least squares; SD: standard deviation
Treatment group comparisons of change from baseline to exit are based on an ANCOVA model with terms for treatment group, region (North America, Europe) and baseline value
Source: ARC003 Clinical Study Report[39]

In contrast to the findings at PALISADE exit, Table 18 shows that following extended Palforzia maintenance therapy using an open-label design in ARC004, [redacted] [65] [redacted] [65]

Parent proxy-reported FAQLQ and FAIM mean change from baseline scores [redacted].[65] Again, this finding was not unexpected, as in very young children HRQoL is generally thought to be less impaired, with caregivers bearing most of the disease burden at this age, and hence there was less scope for

the child's HRQoL to improve.[67] In addition, research on parents of children with a life threatening condition has shown a transition from a protective parenting style in parents of younger children (characterised by attempts to protect the child themselves), to a monitoring parenting style in parents of adolescents (characterised by parents' attempts to provide tools to enable the child to cope by themselves).[89] Parents of younger children may also need more time to process the effect of desensitisation on the risk associated with accidental exposure and to "stand down" from a position of constant vigilance and stress, in effect, to move from the protective to the monitoring parenting style.[67]

Table 18: PALISADE follow-on (ARC004) FAQLQ and FAIM mean change from baseline in total score in participants aged 4 to17 years (safety population)

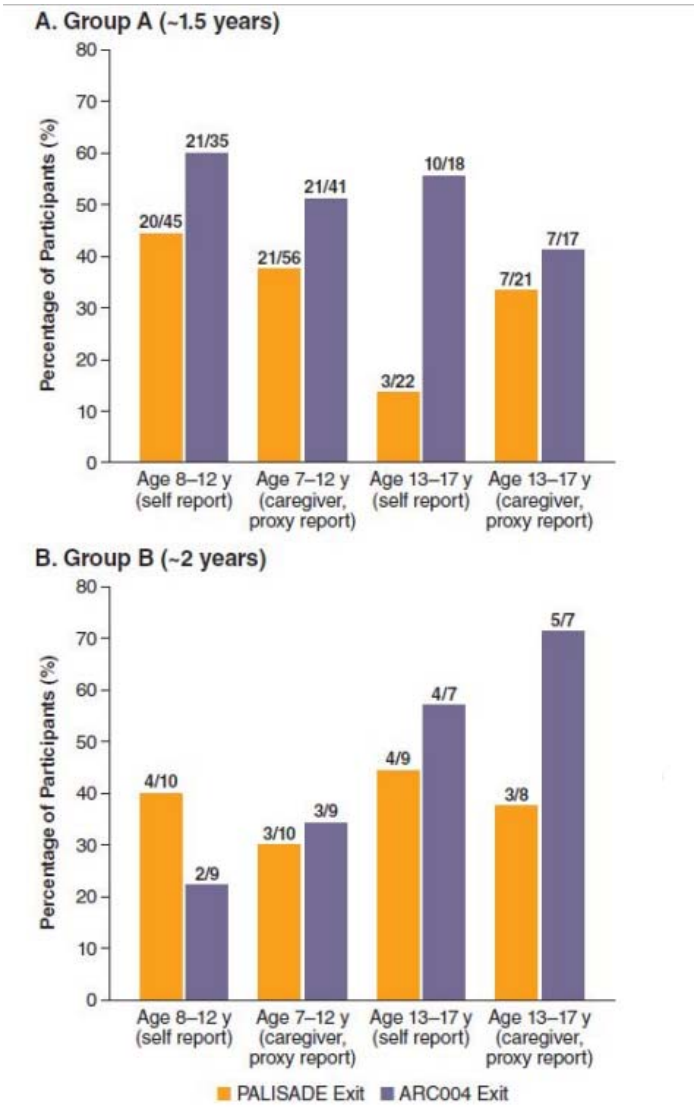
	Cohort 1	Cohort 3A
FAQLQ Total Score*		
Self-reported, participants 8–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Self-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 4–6 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 7–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
FAIM Total Score		
Self-reported, participants 8–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Self-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
FAIM parent expectation of outcomes domain		
Parent proxy-reported, participants 4–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
FAIM child expectation of outcomes domain		
Parent proxy-reported, participants 4–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]

FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; SD: standard deviation.
Source: ARC004 Clinical Study Report[65]

In a further post-hoc exploration of FAQLQ results from PALISADE and ARC004 as part of an overall assessment of efficacy, safety and quality of life with extended Palforzia treatment, an HRQoL responder analysis was conducted based on the assumed MID of 0.5 and noted a trend in increasing proportion of FAQLQ responders with increased duration of therapy (see Figure 21. Note that in Figure 21 Group A is equivalent to ARC004 Cohort 1 and Group B is Cohort 3A).[67] Full tabulated results of the FAQLQ and FAIM responder analysis[67] are available in Table 70 (FAQLQ) and Table 71 (FAIM) in Appendix L).

Although the FAQLQ and FAIM results in ARC004 should be interpreted with caution due to the relatively small number of participants in each subgroup for these measures and due to the open non-comparative design of the study, these findings may indicate a long-term reduction in stress and anxiety associated with the reduced risks of accidental exposure to peanut.[67]

Figure 21: PALISADE follow-on (ARC004) FAQLQ responder analysis (percentage of participants whose FAQLQ total score reduced (i.e. improved) by ≥0.5 points from PALISADE baseline to ARC004 exit)



FAQLQ: Food Allergy Quality of Life Questionnaire
Group A is equivalent to ARC004 Cohort 1 and Group B is Cohort 3A
Source: Fernandez-Rivas et al., 2021[67]

ARTEMIS FAQLQ and FAIM results

FAQLQ and FAIM were assessed in ARTEMIS at the screening visit before blinding and at the exit DBPCFC visit immediately after study unblinding. Longer-term HRQoL of ARTEMIS participants has not yet been assessed.

Participant self-reported and parent proxy-reported FAQLQ and FAIM total score mean change from baseline results are reported in Table 19.

Improvements in HRQoL among those treated with Palforzia were [redacted]. However participants aged 8 to 12 years experienced [redacted] with

significant improvements in FAQLQ versus placebo in “total score” (-1.09 (95% CI: -1.95, -0.22); p=0.015), and for the domains assessing “allergen avoidance and dietary restrictions” (-1.18 [95% CI: -2.06, -0.30]; p=0.011), and “risk of accidental exposure” (-1.20 [95% CI: -2.26, -0.15]; p=0.026)).[37]

However no meaningful improvements were seen in self-reported FAQLQ for participants aged 13 to 17 nor in any of the parent-reported FAQLQ scores.[37] Whilst self-reported FAQLQ scores for 13-to-17-year-olds treated with Palforzia demonstrated a mean change from baseline exceeding the MCID of 0.5, the difference versus placebo was not statistically significant due to the placebo “response”.[37] General improvement may be due to raised patient awareness and knowledge as a result of clinical care during treatment, although this hypothesis has yet to be tested in the context of a clinical trial.

FAIM improvements were observed to varying degrees across domains.[37] Marked improvements in excess of the MID were observed in FAIM domains associated with the likelihood of severe reactions and death as a result of accidental exposure in all Palforzia-treated groups versus baseline and versus placebo, for both self-and caregiver-reported versions. It is thought that the expectations associated with accidental allergen exposure that were addressed in FAIM are more immediately tangible after unblinding than the broader psychosocial aspects (including habitual behaviours) of food allergy covered in the FAQLQ.[37]

Similar to PALISADE results, no worsening that exceeded the MID was reported in any FAQLQ or FAIM domains except for the FAQLQ score for participants on placebo aged 8 to 12 years.[37]

Table 19: ARTEMIS (ARC010) FAQLQ and FAIM mean change from baseline in total score in patients aged 4–17 years (ITT population)

	Palforzia	Placebo
FAQLQ Total Score		
Self-reported, participants 8–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
LS mean difference (Palforzia-placebo) [95% CI]	-1.09 (-1.95, -0.22)	
P-value	0.0154	
Self-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
LS mean difference (Palforzia-placebo) [95% CI]	[redacted]	

P-value	
Parent proxy-reported, participants 4–6 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	-0.30 (-1.10, 0.49)
P-value	0.4463
Parent proxy-reported, participants 7–12 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	-0.09 (-0.74, 0.57)
P-value	0.7872
Parent proxy-reported, participants 13–17 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	-0.32 (-0.95, 0.31)
P-value	0.2970
FAIM Total Score	
Self-reported, participants 8–12 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	
P-value	
Self-reported, participants 13–17 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	
P-value	
Parent proxy-reported, participants 4–12 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	
P-value	
Parent proxy-reported, participants 13–17 years	
Mean change from baseline (SD)	
LS mean difference (Palforzia-placebo) [95% CI]	
P-value	

ANCOVA: analysis of covariance; CI: confidence interval; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; ITT: intention-to-treat; LS: least squares; SD: standard deviation
Treatment group comparisons of change from baseline to exit are based on an ANCOVA model with terms for treatment group, country and baseline value
Source: O'Hourihane et al., 2020[37]; ARC010 Clinical Study Report[76]

HRQoL findings from the clinical trials are supported by the quality-of-life and utility survey conducted by Aimmune Therapeutics among UK peanut-allergic patients and their caregivers. See Section B.3.4.4 for details on the utility study and its use in informing the cost-effectiveness model. The full study report for the utility study is available in Appendix P.

Treatment satisfaction reported in PALISADE, ARC004 and ARTEMIS (TSQM-9)

Treatment satisfaction using the validated Treatment Satisfaction Questionnaire for Medication (TSQM-9)[90] was assessed after the exit DBPCFC and unblinding in PALISADE and ARTEMIS, and at study exit in ARC004. Although treatment satisfaction is not a measure of HRQoL per se, the TSQM-9 results help to give context to the HRQoL results described above and demonstrate that despite some inconvenience due to treatment and a level of commitment required, patients and caregivers perceive that the benefits of treatment (namely reduced risk of peanut allergy and improved HRQoL) outweigh the drawbacks.

The questionnaire was designed to be used with participants on treatment, and was therefore completed by those on the Palforzia rather than placebo arm of the pivotal studies, and also by participants exiting the studies early.

Description of the TSQM-9

TSQM-9 is a validated 9-item instrument designed to assess patient-reported treatment satisfaction with medication across 3 domains, namely effectiveness, convenience and global satisfaction with treatment. Each domain is comprised of 3 items that are scored on a 5- or 7-point scale with scores ≥3 or ≥4 indicating satisfaction, respectively. Composite total scores are calculated from each domain and normalised on a 0–100 scale with scores ≥60% indicating satisfaction[91]. TSQM-9 is designed for participants who have received active treatment and has been used in trials investigating asthma, atopic dermatitis, arthritis, multiple sclerosis and others.[91-94]

The original TSQM 14-item questionnaire is available within a publication by Atkinson et al.[95] The more recent short-form TSQM-9 omits questions 4 through 8 of this questionnaire although it still retains good scale reliability and validity.[90]

Results of TSQM-9 in PALISADE, ARC004 and ARTEMIS

Mean total scale scores were consistent across all studies, and indicated treatment satisfaction in all domains (Table 20). Specifically, although moderate satisfaction was reported with the convenience of Palforzia treatment (mean scores by individual study between [redacted] and [redacted], on a scale of 0-100), participants reported high global satisfaction

(mean scores [redacted]) and high confidence in the effectiveness of treatment (mean scores [redacted]).[39,65,76]

Moreover, on a scale of 1 to 5, participants expressed strong certainty that the good things about the medication outweigh the bad (mean scores across studies for this item were in the range [redacted] out of a maximum of 5).[39,65,76]

Table 20: Treatment satisfaction (TSQM-9 domain scores) at PALISADE, ARC004 and ARTEMIS exit (Palforzia and early exiting participants only)

	PALISADE exit	ARC004 Cohort 1 exit	ARC004 Cohort 3A exit	ARTEMIS exit
Participants completing at least one or more questions of the TSQM-9 (n)	[redacted]	[redacted]	[redacted]	[redacted]
TSQM-9 Domain				
Effectiveness (mean score on scale 0-100, (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Convenience (mean score on scale 0-100, (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Global satisfaction (mean score on scale 0-100, (SD)	[redacted]	[redacted]	[redacted]	[redacted]

SD: standard deviation; TSQM-9: Treatment Satisfaction Questionnaire for Medication-9
Domain scores above 60 are deemed to indicate satisfaction.[94]
Source: ARC003[39], ARC004[65] and ARC010[76] Clinical Study Reports.

B.2.7 Subgroup analysis

Overall, a-priori and post-hoc subgroup efficacy analyses in the two phase 3 pivotal trials (PALISADE and ARTEMIS) showed no clinically significant differences between subgroups. No subgroup of paediatric participants was identified that would benefit more from treatment than other subgroups. See Appendix E for further details.

ARC003 (PALISADE)

Supportive analyses to the primary and key secondary efficacy endpoint analysed paediatric subgroups in the ITT and completer populations by geographic region (North America region, Europe region) and by age group (4 to 11 years, 12 to 17 years), and by geographic region and age group (North America region 4 to 11 years, 12 to 17 years; Europe region 4 to 11 years, 12 to 17 years). [redacted]

[redacted] (Table 21). Results of the supportive analyses for the primary efficacy endpoint are presented in Table 21 below for the ITT population. Full results for the primary efficacy endpoint are available in Appendix E.

Table 21: PALISADE (ARC003) Supportive analyses for the primary efficacy endpoint

	Palforzia	Placebo
Supportive analysis by region (ITT population)		
Europe region	[redacted]	[redacted]
Response rate (95% CI), 4 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
North America region	[redacted]	[redacted]
Response rate (95% CI), 4 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Supportive analysis by paediatric age group (ITT population)		
Aged 4 to 11 years	[redacted]	[redacted]
Response rate (95% CI), 4 to 11 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Aged 12 to 17 years	[redacted]	[redacted]
Response rate (95% CI), 12 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Supportive analysis by region and paediatric age group (ITT population)		
Europe region aged 4 to 11 years	[redacted]	[redacted]
Response rate (95% CI), 4 to 11 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Europe region aged 12 to 17 years	[redacted]	[redacted]
Response rate (95% CI), 12 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
North America region aged 4 to 11 years	[redacted]	[redacted]
Response rate (95% CI), 4 to 11 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
North America region aged 12 to 17 years	[redacted]	[redacted]
Response rate (95% CI), 12 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	

P-value	[redacted]

CI: confidence interval; ITT: intention-to-treat.
Source: ARC003 Clinical Study Report Error! Reference source not found.

ARC010 (ARTEMIS)

The primary efficacy analysis was repeated for the ITT population age subgroups of 4 to 11 years and 12 to 17 years.[76] [redacted] [76] Analyses for the primary efficacy endpoint in participants aged 4 to 11 years and 12 to 17 years are presented below for the ITT population (Table 22). Results for the primary efficacy endpoint in participants aged 4 to 17 years by country and in participants in the completer population are available in Appendix E.

Table 22: ARTEMIS (ARC010) Supportive analyses for the primary efficacy endpoint

	Palforzia	Placebo
Supportive analysis by paediatric age group (ITT population)		
Aged 4 to 11 years	[redacted]	[redacted]
Response rate (95% CI), 4 to 11 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	
Aged 12 to 17 years	[redacted]	[redacted]
Response rate (95% CI), 12 to 17 years	[redacted]	[redacted]
Treatment difference (Palforzia-placebo) [95% CI]	[redacted]	
P-value	[redacted]	

CI: confidence interval; ITT: intent-to-treat
Source: ARC010 Clinical study report[76]

B.2.8 Meta-analysis

Due to differences in study design (see Table 23), Aimmune determined it was not appropriate to conduct a meta-analysis or pooling of efficacy data from across the trials.

Table 23: Key differences in conduct between PALISADE and ARTEMIS trials

Study Design Element	PALISADE	ARTEMIS	Rationale for Difference in Study Design
Location	US, Canada, Europe (UK, Ireland, Germany, Spain, Italy, Sweden, Denmark, Netherlands)	Europe: UK, Ireland, Germany, Spain, Italy, Sweden, France	Add more European regional experience to database
Age group	4 to 55 years	4 to 17 years	To fulfil the PIP requirements
Inclusion DBPCFC	Sensitive to 100 mg or less peanut protein	Sensitive to 300 mg or less peanut protein	Variability in sensitivity and investigator feedback based on screen failures in ARC003
Duration of maintenance	6 months	3 months	Understand time course of desensitisation more accurately

DBPCFC: double-blind, placebo-controlled food challenge; PIP: paediatric investigational plan; US: United States; UK: United Kingdom.

As discussed in the cost-effectiveness section (see Section B.3.3), given the need to populate the model transition matrices with detailed patient-level efficacy data, a meta-analysis of key endpoints would not have been sufficient to populate the model.

Pooling PALISADE and ARTEMIS data at a patient level was considered but was discounted, primarily due to the different lengths of the maintenance periods across the studies. The rationale and decision not to pool the studies for efficacy was accepted by the EMA and FDA. Moreover, efficacy results of PALISADE and ARTEMIS are consistent, with a large, highly statistically significant treatment difference in both studies versus placebo, hence pooling would add little to the interpretation of results. As discussed in the cost-effectiveness section (see Section B.3.8.4), results of the cost-effectiveness model using each trial individually are similar.

Safety data has, however, been pooled across Palforzia pivotal and extension trials (Section B.2.10.3). Since serious adverse events were rare across individual trials, it was surmised that pooling may add more insight into the rates of such events due to the larger cohort of patients.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were undertaken.

B.2.10 Adverse events

2.10.1 Clinical trials reporting safety outcomes

Safety was assessed in the PALISADE (ARC003), ARC004 follow-on, and ARTEMIS (ARC010) trials. Safety outcomes included treatment-emergent adverse events, (TEAEs) which include all the adverse events appearing or worsening while on treatment, (regardless of the relatedness or not to the treatment), anaphylactic reactions (including anaphylaxis), use of adrenaline as a rescue medication for allergic reactions, assessment of lung function, physical examination of the participant and assessment of the participant's vital signs.

2.10.2 Adverse events reported in the PALISADE, ARC004 and ARTEMIS RCTs

TEAEs were assessed during the Palforzia trials. TEAEs are defined as all-cause adverse events occurring during treatment. Treatment-related adverse events (TRAEs) are a subset of TEAEs related specifically to treatment as determined by the investigator.

Note that all-cause TEAEs are the focus of the safety analyses below, however only TRAEs are used in the cost-effectiveness model to ensure only relevant cost and QALY impacts are taken into account. Additionally, as noted previously, adverse reactions due to accidental exposure to peanut are included in the model separately to TRAEs, as an indicator of treatment efficacy rather than safety.

TEAEs (whether related or not to the treatment) reported in the PALISADE, ARC004 and ARTEMIS trials are summarised in Table 24 and Table 25.

Table 24: Summary of key safety outcomes in participants 4 to 17 years of age – ARC003 and ARC004

Participants with a treatment-emergent adverse event (TEAE), n (%)	PALISADE (ARC003)		PALISADE follow-on (ARC004) (N=140; Daily dosing Cohorts 1 and 3A)
	Palforzia (N=372)	Placebo (N=124)	
Participants with ≥1 TEAE	367 (98.7%)	118 (95.2%)	-
Abdominal pain	194 (52.2%)	30 (24.2%)	16 (11.4%)
Vomiting	154 (41.4%)	30 (24.2%)	24 (17.1%)
Upper abdominal pain	152 (40.9%)	26 (21.0%)	14 (10.0%)

Oral pruritus	151 (40.6%)	20 (16.1%)	10 (7.1%)
Nausea	146 (39.2%)	29 (23.4%)	14 (10.0%)
Oral paresthesia	65 (17.5%)	8 (6.5%)	-
Lip swelling	38 (10.2%)	5 (4.0%)	-
Cough	152 (40.9%)	42 (33.9%)	24 (17.1%)
Throat irritation	152 (40.9%)	34 (27.4%)	20 (14.3%)
Rhinorrhoea	113 (30.4%)	28 (22.6%)	10 (7.1%)
Sneezing	98 (26.3%)	18 (14.5%)	11 (7.9%)
Throat tightness	86 (23.1%)	8 (6.5%)	-
Dyspnoea	44 (11.8%)	5 (4.0%)	-
Dysphonia	25 (6.7%)	2 (1.6%)	-
Pruritus	153 (41.1%)	34 (27.4%)	8 (5.7%)
Urticaria	143 (38.4%)	30 (24.2%)	23 (16.4%)
Rash	81 (21.8%)	18 (14.5%)	7 (5.0%)
Chest discomfort	24 (6.5%)	1 (0.8%)	-
Anaphylactic reaction	53 (14.2%)[†]	4 (3.2%)	12 (8.6%)
Ear pruritus	35 (6.7%)	0	-
Pyrexia	[redacted]	[redacted]	28 (20.0%)
Headache	[redacted]	[redacted]	20 (14.3%)
Upper respiratory tract infection	[redacted]	[redacted]	23 (16.4%)
Oropharyngeal pain	[redacted]	[redacted]	14 (10.0%)
Nasopharyngitis	[redacted]	[redacted]	10 (7.1%)
Nasal congestion	[redacted]	[redacted]	10 (7.1%)
Viral infection	[redacted]	[redacted]	14 (10.0%)
Diarrhoea	[redacted]	[redacted]	9 (6.4%)
Participants with ≥1 TEAE (by maximum severity)			
Mild	129 (34.7%)	62 (50.0%)	73 (52.1%)
Moderate	222 (59.7%)	55 (44.4%)	41 (29.3%)
Severe	16 (4.3%)	1 (0.8%)	3 (2.1%)
Participants with ≥1 anaphylactic reaction (by maximum severity)			
Mild	23 (6.2%)	1 (0.8%)	3 (2.1%)
Moderate	29 (7.8%)	3 (2.4%)	7 (5.0%)
Severe (anaphylaxis)	1 (0.3%)	0 (0.0%)	2 (1.4%)
Participants with ≥1 serious/severe TEAE	21 (5.6%)	2 (1.6%)	0
Withdrawals from trial due to TEAEs, total and by category	43 (11.6%)	3 (2.4%)	3 (2.1%)
Acute/chronic/ recurrent GI	24 (6.5%)	2 (1.6%)	-
Anaphylactic reactions[‡]	7 (1.9%)	0	-
Respiratory system	11 (3.0%)	3 (2.4%)	-
Skin and subcutaneous	5 (1.3%)	2 (1.6%)	-
Other	14 (3.8%)	0	-

GI: gastrointestinal; TEAE: treatment-emergent adverse event
[†] Events of anaphylactic reaction included one case of severe anaphylaxis in the active-drug group during the maintenance phase.
[‡]Investigator-identified anaphylactic reactions events (1 severe in PALISADE)
Source: Vickery et al. 2018;[38] Vickery et al. 2020[64]

Table 25: Summary of key safety outcomes – ARTEMIS (ARC010)

Participants with a treatment-emergent adverse event (TEAE), n (%)	Palforzia (N=132)	Placebo (N=43)
Participants with ≥1 TEAE	130 (98.5%)	42 (97.7%)
GI disorders	120 (90.9%)	33 (76.7%)
Abdominal pain	88 (66.7%)	19 (44.2%)
Nausea	58 (43.9%)	11 (25.6%)
Vomiting	53 (40.2%)	10 (23.3%)
Paraesthesia oral	52 (39.4%)	9 (20.9%)
Oral pruritus	28 (21.2%)	1 (2.3%)
Abdominal discomfort	17 (12.9%)	2 (4.7%)
Lip pruritus	16 (12.1%)	2 (4.7%)
Abdominal pain upper	14 (10.6%)	5 (11.6%)
Respiratory, thoracic, & mediastinal disorders	112 (84.8%)	34 (79.1%)
Cough	66 (50.0%)	24 (55.8%)
Throat irritation	57 (43.2%)	8 (18.6%)
Sneezing	43 (32.6%)	7 (16.3%)
Wheezing	22 (16.7%)	3 (7.0%)
Dyspnoea	15 (11.4%)	3 (7.0%)
Skin and subcutaneous tissue disorders	100 (75.8%)	(65.1%)
Pruritus	67 (50.8%)	14 (32.6%)
Urticaria	48 (36.4%)	9 (20.9%)
Immune system disorders	28 (21.2%)	5 (11.6%)
Anaphylactic reaction*	16 (12.1%)	1 (2.3%)
Participants with ≥1 TEAE (by maximum severity)		
Mild	66 (50%)	24 (56%)
Moderate	63 (48%)	18 (42%)
Severe or higher	1 (1%)	0
Participants with ≥1 anaphylactic reaction (by maximum severity)		
Mild	8 (6%)	1 (2%)
Moderate	8 (6%)	0
Severe† (anaphylaxis)	0	0
Participants with ≥1 serious TEAE†	1 (1%)	2 (5%)
Mild	1 (1%)	1 (2%)
Moderate	0	1 (2%)
Severe or higher	0	0
Withdrawal from trial due to TEAEs, total and by category	14 (11%)	1 (2%)
Acute/chronic/recurrent GI	9 (6.8%)	1 (2.3%)
Respiratory system	6 (4.5%)	0
Cutaneous	3 (2.3%)	0
Anaphylactic reactions	1 (0.8%)	0
Other	3 (2.3%)	1

GI: gastrointestinal; TEAE: treatment-emergent adverse event.
*All reported anaphylactic reactions were mild or moderate in severity. No anaphylaxis (severe anaphylactic reaction) was reported.
† Severe anaphylactic reaction, as per regulatory guidance
Source: Hourihane et al., 2020[37]

2.10.3 Pooled safety data across pivotal RCTs: integrated safety population

Pooled safety data are reported for the integrated safety population (Table 26 and Figure 22; see also Table 18 in Appendix F). The integrated safety population included all participants aged 4 to 17 years receiving at least one dose of Palforzia during the 3 phase 3 trials (PALISADE, ARTEMIS and RAMSES) and/or two follow-on studies (ARC004, ARC011).

The safety data of participants on placebo were not included in the integrated safety population.

Data are reported in the Palforzia EPAR report, but at the time of that report, ARC004 and ARC011 trials were still ongoing. Results for these two studies were included up to the data cut-off date of 15 December 2018 (Table 26).[66,77]

Table 26: Overall summary of treatment-emergent adverse events (TEAEs, related or not) in the integrated safety population

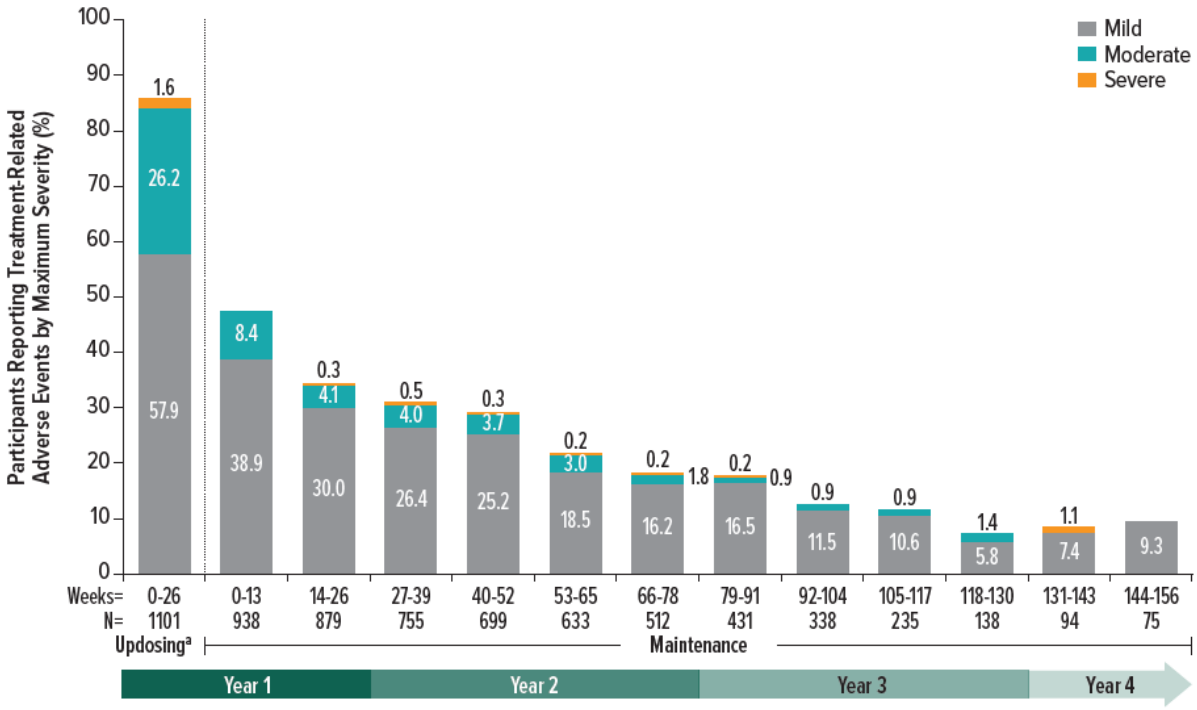
	Initial dose escalation (N=944)	Up-dosing (N=919)	300 mg/day (any weeks) (N=770)	Overall (any dose) (N=944)
Participants with ≥1 TEAE (by maximum severity)	481 (51.0%)	891 (97.0%)	687 (89.2%)	933 (98.8%)
Mild	426 (45.1%)	438 (47.7%)	446 (57.9%)	373 (39.5%)
Moderate	54 (5.7%)	430 (46.8%)	226 (29.4%)	522 (55.3%)
Severe	1 (0.1%)	22 (2.4%)	15 (1.9%)	37 (3.9%)
Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Death	0	0	0	0
Participants with TRAEs	426 (45.1%)	788 (85.7%)	444 (57.7%)	851 (90.1%)
Participants with ≥1 serious TEAE	0	7 (0.8%)	8 (1.0%)	14 (1.5%)
Mild	0	2 (0.2%)	0	1 (0.1%)
Moderate	0	3 (0.3%)	4 (0.5%)	7 (0.7%)
Severe	0	1 (0.1%)	4 (0.5%)	5 (0.5%)
Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Death	0	0	0	0
Withdrawal from trial due to AEs*	20 (2.1%)	80 (8.7%)	9 (1.2%)	108 (11.4%)
Participants with ≥1 anaphylactic reaction	6 (0.6%)	80 (8.7%)	76 (9.9%)	143 (15.1%)

AE: adverse event; SAE: serious adverse event; TEAE/TRAE: treatment-emergent/related adverse event.
*Overall, 3 participants discontinued Palforzia due to anaphylaxis (severe anaphylactic reaction)
15 December, 2018 data cutoff for ARC004 and ARC011 trials
Source: Palforzia EPAR report[66]

A submitted manuscript, which is currently under review, included the [redacted].[77]

An additional analysis of the pooled safety population including not only the finished trials, but also the ongoing ARC008 trial (data cut-off July 31, 2020) was presented in February 2021, and included safety data from patients with up to 3.5 years of exposure to Palforzia.[96] This analysis shows that mild to moderate TRAEs were often experienced early in treatment, but both incidence and severity of TRAEs declined with prolonged treatment (Figure 22).

Figure 22: Proportion of participants reporting any treatment-related adverse event by maximum severity (integrated safety population)



a Actual time of updosing was variable across trials
Initial dose escalation was not included due to the very short duration (2 days) and intensive in-clinic visit.
31 July, 2020 data cutoff for ARC008 trial, all other trials final.
Source: Casale et al. AAAAI 2021[96]

2.10.4 Overview of safety results

Since Palforzia is a peanut-based treatment containing the allergens to which peanut-allergic individuals are highly sensitised, allergic symptoms and reactions are an expected consequence of the use of Palforzia.

Overall, the safety profile of Palforzia in participants aged 4 to 17 years appears acceptable with no unexpected safety signals. Data from the placebo-controlled trials indicate that, with the exception of a higher frequency of hypersensitivity reactions in

Palforzia-treated participants, which was expected, there was a similar safety profile between the active and placebo arms (Table 24, Table 25).

The incidence of TEAEs was higher during up-dosing phase (85.7%) (Table 26 and Figure 22), with their frequency decreasing over time during the maintenance phase (57.7%; Table 26 and Figure 22). In the majority of cases, adverse reactions to Palforzia were mild to moderate (Table 26 and Figure 22).

As expected, because of the oral route of administration, the most common adverse reactions (of any severity) were mostly gastrointestinal: abdominal pain (49.4%), throat irritation (40.7%), pruritus (33.7%), nausea (33.2%), vomiting (28.5%), urticaria (28.5%), oral pruritus (26.0%), abdominal discomfort (22.9%), and abdominal pain upper (22.8%).[1,66]

The timing of TRAEs was generally predictable and they usually resolved quickly. The median time from administration of Palforzia in the clinic to onset of the first symptom ranged from 4 to 8 minutes. The median time from onset of the first symptom to resolution of the last symptom ranged from 15 to 30 minutes.[1] [redacted][77]

Treatment discontinuation of Palforzia due to ≥1 adverse reaction occurred in 11.4% of participants (Table 26). The most common adverse reactions leading to discontinuation of treatment were abdominal pain (3.8%), vomiting (2.5%), nausea (1.9%), and anaphylactic reaction (1.6%), including anaphylaxis.[66]

As evidenced by results from the PALISADE follow-on study (ARC004; Table 24) and the pooled safety analysis for the integrated population (Figure 22), adverse events related to Palforzia treatment became milder and less frequent over time, due to the gradual process of desensitisation. The safety profile of Palforzia is consistent across trials, well characterised, manageable and improves over time.

B.2.11 Ongoing studies

No ongoing studies will provide additional evidence in the 12 months following this appraisal. The ARC008 long-term extension study is continuing but new data are not anticipated until approximately 2024.

Transition to peanut in diet

As is stated within Palforzia's licence, '*[…] daily maintenance is required to maintain the tolerability and clinical effects of Palforzia. Efficacy data are currently available for up to 24 months of treatment and no recommendation can be made about the duration of treatment beyond 24 months. The effect of stopping treatment on maintenance of clinical efficacy has not been evaluated*.' In relation to real-life clinical practice, Aimmune Therapeutics understands from several clinical experts that once patients are deemed sufficiently desensitised, they would envisage transitioning most patients onto an alternative to licensed treatment – namely regular intake of peanut in diet. As patients would be desensitised but ultimately still allergic (i.e. not 'cured' of their peanut allergy), in order to maintain desensitisation, experts considered that patients would need to regularly ingest a certain amount of peanut – e.g. a peanut kernel or 'M&M' each day – with the amount and the timing of this transition being advised by the clinician. Just as before, patients would still need to carry an AAI and undertake a strict avoidance diet.

Transitioning from Palforzia to regular intake of peanut in diet has not been studied in clinical trials by Aimmune Therapeutics, and there is limited evidence available on the success of introducing peanut into diet post-desensitisation, although long-term follow-up of two trial programmes (peanut OIT combined with probiotic (PPOIT) trial[97,98] and the DEVIL study[99]) have demonstrated some success with continuation of regular intake of peanut in diet. However, in order to understand this potential approach in more detail in relation to Palforzia and to be able to best reflect real life clinical practice in cost-effectiveness modelling, Aimmune Therapeutics undertook a structured expert elicitation exercise with UK clinical experts in March 2021 (Sheffield Elicitation Framework (SHELF) Elicitation). Further details of the SHELF Exercise are provided in Appendix N but in summary, the SHELF Elicitation panel of experts advised that, [redacted]

Aimmune Therapeutics continues to explore the optimal treatment duration through longer-term clinical trials but in the meantime, outputs from the SHELF Elicitation are incorporated within the cost-effectiveness modelling represented within this dossier (see Section B.3.3.6).

B.2.12 Innovation

Palforzia, as the first licensed immunotherapy, represents a potential step change in the management of peanut allergy. There are currently no other licensed therapies for peanut allergy in Europe, avoidance alone is not a treatment strategy and there remains a significant unmet need.

Palforzia is the first application of an OIT to provide both a standardised product and structured dosing protocol for desensitisation to peanut with efficacy supported by two pivotal multicentre Phase 3 trials demonstrating Palforzia's efficacy in desensitising participants to peanut protein.

Based on the data from the Phase 2 clinical trials, Palforzia was granted Breakthrough Designation by the FDA.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Designed in line with global regulatory requirements, the landmark Palforzia clinical trial programme is the largest conducted to date in peanut allergy, enrolling 1292 participants aged 4 and older across 11 countries (Europe and North America), including several centres in the UK.

The Palforzia clinical trial programme demonstrated:

- ***Clinically meaningful efficacy of Palforzia, relevant to the UK peanut allergic population and treatment setting***

Overall, inclusion and exclusion criteria in the PALISADE (ARC003) and ARTEMIS (ARC010) trials were appropriate and enrolled participants were representative of the UK peanut-allergic population. In the ARTEMIS trial, peanut protein sensitivity cut-off was 300 mg, allowing to extend recruitment to a broader population than PALISADE.[37]

The primary efficacy endpoint was desensitisation to peanut, which was objectivised in a DBPCFC, accepted as a proxy for an allergic reaction to accidental exposure.[70] Whilst not used in day to day clinical practice, assessing DBPCFC at baseline and study exit in a double-blind RCT is currently the only feasible way to assess efficacy in terms of desensitisation and infer any associated changes in risk.[37] The primary efficacy endpoint (% participants who tolerated a single dose of ≥1000 mg peanut protein without dose-limiting symptoms) was met in the two RCTs with treatment differences (versus placebo) of 47.8% ($p<0.0001$) in PALISADE and 56.0% ($p<0.0001$) in ARTEMIS, demonstrating that Palforzia treatment results in clinically meaningful desensitisation to peanut protein. As most peanut-allergic individuals react to minimal amounts of peanut protein, tolerating 300 mg is considered the minimal clinically relevant threshold, as this value is above most labelled trace amounts of peanut protein in pre-packaged food, and above the median amount of peanut protein triggering reactions in real life.[27] Tolerating 1000 mg enhances clinical relevance to an important level, as this would reflect amounts of peanut protein in self-made food which are likely higher than 300 mg,[66] and also ensure that patients are still able to tolerate a clinically meaningful amount of peanut while having cofactors, as illness or sleep deprivation. In addition, Palforzia reduced symptom frequency and severity due to peanut exposure. The follow-on study (ARC004) showed that protection against allergic reactions continues to improve with increased duration of treatment.

- ***Significant patient HRQoL benefits and a high level of treatment satisfaction due to successful desensitisation with Palforzia***

Peanut allergy can have a significant and, in some respects unique, impact on the HRQoL of patients and their families.[54,57] However, measuring HRQoL in peanut allergy clinical trials presents some challenges. Peanut allergy (and food allergy more generally) is unique among many chronic diseases because it is largely an asymptomatic condition, unless the patient is exposed to the allergen, which can have potentially devastating consequences. HRQoL in peanut allergy is not driven by daily or frequent symptoms, and day to day level of risk cannot be checked through any measures or tools which would allow for perception of changes in health status by

patients. Instead, it is driven by patient beliefs and expectations about the risk of anaphylaxis occurring and the expected benefits of any interventions that reduce this risk.

As such, during blinded trials, significant improvements in patient HRQoL due to treatment are not anticipated, as the patient is blinded to their level of risk of anaphylaxis and thus their threat perception remains constant. Although FAQLQ was measured before blinding at start of PALISADE and ARTEMIS and immediately after the DBPCFC and unblinding at the end of the studies, the researchers did not anticipate a significant improvement in HRQoL at unblinding even with successful treatment, as it takes time for patients and families to adjust to the knowledge and to the real-world benefits of their new desensitised health state.

In line with the above expectation, whilst the short-term FAQLQ data collected in the blinded pivotal trials showed relatively limited HRQoL benefit at study exit, patients evaluated after ~1.5 and ~2 years of daily Palforzia treatment in the open label ARC004 extension study experienced continued improvements in FAQLQ scores.[67] The same pattern of meaningful HRQoL benefit observed only after unblinding has been documented in other blinded peanut immunotherapy clinical studies.[100,101] Conversely in a recent open-label, controlled food OIT trial, a design arguably more aligned with a real-life setting, significant FAQLQ improvements were seen at an earlier stage of treatment, upon reaching maintenance dosing, with continued improvement 6 months later.[102] It may be that both blinded and open label design studies are needed to provide a more detailed picture of HRQoL impact.

The important HRQoL benefits observed with Palforzia treatment were also supported by Palforzia-treated patients and their caregivers consistently expressing high treatment satisfaction in all studies, as measured by the TSQM-9.[103] Furthermore, quotes collected from UK Palforzia trial participants as part of Aimmune's recent utility survey study, as well as from ARC002 phase 2 qualitative exit interviews, serve to illustrate the transformational nature of Palforzia for patients and families who have been successfully treated (see

Figure 23 for illustrative quotes and also Appendix P for the utility study report, which includes ARC002 qualitative exit interview findings).

Figure 23: Illustrative quotes from Palforzia-treated patients and their caregivers (UK utility study and US ARC002 qualitative exit interviews)

"I didn't really know what the study was going to do, how much I'd be able to eat by the end of it but I wasn't expecting it to get this much better because it's made me a lot less anxious about everything, so that's really helpful." *[adolescent, UK]*

"… emotionally he's much happier, he can also go to different sporting events and that makes him much happier. He feels like a boy again." *[caregiver, US]*

"I don't have that fear of her having accidental exposure and dying, that was a pretty scary thing that I carried with me before" *[caregiver, US]*

…It's life changing. It's all a bit cliché but it means she will have a different teenage experience to the one she might have had, and she won't have to worry for the rest of her life about it. It's brilliant." *[Caregiver, UK]*

In summary, within the clinical trials it was possible to demonstrate meaningful HRQoL improvements with Palforzia treatment, despite an anticipated masking effect during the blinded phases of the trials, although this effect may have led to lower reported HRQoL short-term benefits than would be expected to be seen in a real-life treatment context.

- ***A manageable and expected safety profile, with treatment-related adverse events reducing with duration of treatment***

Overall, Palforzia's safety profile in patients 4–17 years is manageable with no unexpected safety signals for a desensitisation OIT. The reported TRAEs are a consequence of the immunomodulatory effect of Palforzia, which is a peanut-based treatment given to peanut-sensitive individuals. Thus, hypersensitivity reactions (allergic reactions or symptoms) are expected and improve with the process of gradual desensitisation. In the clinical trials, most TRAEs are mild and moderate, occur most commonly in temporal proximity to the OIT dose and are generally easily managed and resolve quickly. In comparison to unpredictable anaphylactic reactions following accidental exposure to peanut, anaphylactic reactions related to Palforzia occur when the patient and their caregiver(s) are more likely to be prepared for a possible reaction, as they mostly occur near the time of dosing.

Furthermore, long-term studies indicate that TRAEs reduce substantially with extended duration of treatment (Figure 22).

B.3 Cost effectiveness

- A Markov model based on different peanut protein tolerance health states and data from the Palforzia pivotal trials was used to evaluate the cost-effectiveness of Palforzia for patients with peanut allergy.
- A cost-effectiveness analysis was conducted to compare Palforzia (in combination with avoidance) versus avoidance alone.
- In base case analyses Palforzia was cost-effective versus avoidance, with an incremental cost-effectiveness ratio (ICER) of **£23,142 per QALY**.
- Deterministic sensitivity analyses demonstrated that the cost-effectiveness results were robust to changes in model parameters, with the majority of scenarios remaining cost-effective, and ICERs remaining <£30,000 per QALY (range £15,275–44,490 per QALY).
- In probabilistic sensitivity analysis there was a 38.3% probability of Palforzia being cost-effective versus avoidance at a willingness-to-pay threshold of £20,000 per QALY, and **a 64.4% probability** of Palforzia being cost-effective versus avoidance at a willingness-to-pay threshold of **£30,000 per QALY**
- Palforzia remained cost-effective in scenario analyses which varied key model parameters, with the majority of scenario analyses resulting in ICERs <£30,000 per QALY.
- Consequently, Palforzia is likely to be a cost-effective use of NHS resources for the treatment of peanut allergy.

B.3.1 Published cost-effectiveness studies

- Details of the search, the identified studies, and quality assessments are provided in Appendix G.

Economic studies relevant to the decision problem were identified in a SLR, designed to identify studies that evaluated the cost-effectiveness of therapies used in peanut allergy treatments.

The search identified 15 published cost-effectiveness studies, of which none were conducted from a UK perspective.

The Institute for Clinical and Economic Review in the US market (ICER-US) performed a cost-effectiveness assessment of Palforzia in comparison to avoidance (results of the model were described in two publications: the ICER-US model[104] and Tice et al. [2020][105]). Lifetime cost-effectiveness from a U.S. health care sector perspective using a Markov model was assessed. Using the estimated US price for Palforzia ($4,200/year), the incremental cost-effectiveness ratio was $88,000/QALY. In the ICER-US analysis also Viaskin-Peanut was assessed. Using the estimated price for

Viaskin Peanut ($6,500/year), the incremental cost-effectiveness ratio (ICER) was $216,000/QALY.

In two published cost-effectiveness studies it was estimated that peanut OIT is a cost-effective option in comparison to avoidance in the US (peanut OIT dominates avoidance;[106] ICER=$2,142[107]). However, in another study neither epicutaneous immunotherapy (EPIT) nor peanut OIT was cost-effective in the base model (ICER was $216,061 for EPIT and $255,431 for peanut OIT compared with no treatment).[108]

Other identified analyses were assessing different adrenaline use strategies[109-112] and interventions used in peanut allergy diagnosis.[113]

The details of the search, all the identified studies, and quality assessments are reported in Appendix G.

B.3.2 Economic analysis

There are no previous NICE technology appraisals for peanut allergy nor for food allergy more broadly. Pharmalgen, for the treatment of bee and wasp venom allergy[114], was noted as potentially having some parallels with paediatric food allergy OIT, but due to several differences (e.g. environmental allergy versus food allergy, model based on severity of anaphylactic reactions, adult versus paediatric indication) it is not considered relevant to this submission.

Of the studies identified by the cost-effectiveness SLR, there were three unique model structures. Of the model structures identified, all used a Markov model of which two used a microsimulation.[106,107,109,113,115] Cycle length was not stated in any study and only two studies reported the health states that were used; both were structured around the incidence of peanut allergy-related events and the use of medical resources.[107,109]

In addition, ICER-US performed a cost-effectiveness assessment of Palforzia and Viaskin-Peanut.[104] In their assessment, a Markov model structure with the following health states was used: on-treatment, untreated with peanut sensitivity, peanut tolerant, peanut desensitised and death. A weekly cycle length was used in the first year, with subsequent cycles having a duration of 1 year.[104]

For the purposes of this submission, a *de novo* cohort model with Markov structure was built to reflect the Palforzia pivotal clinical trials (PALISADE and ARTEMIS), with similar health states to those in the ICER-US model.

Results from the PALISADE trial and its follow-on study (ARC004) were used to populate the model in the base case. The ARTEMIS trial extrapolated using ARC004 data was used in scenario and sensitivity analyses (See Section B.2.3 for further information on clinical outcomes).

3.2.1 Summary

Table 27: Summary of the model specification

Variable	Details	Justification/Comments
Population	Children and adolescents with peanut allergy aged 4 to 17 years. Treatment can be continued beyond the age of 17 years.	As per the primary efficacy population of PALISADE and ARTEMIS studies (see Section B.3.3.1). This is also in line with the UK licence.
Treatment	Palforzia (AR101) in combination with avoidance	As per the UK licence and also PALISADE and ARTEMIS studies
Comparators	Avoidance only	Currently standard of care in UK and all European markets as there are no MHRA or EMA-approved treatment options for peanut allergy
Perspective	NHS England and PSS	As per the NICE reference case[116]
Discounting	3.5% for costs and outcomes	As per the NICE reference case[116]
Time horizon	Lifetime (90 years = 100 minus 10)	Due to chronic nature of peanut allergy. In line with previously published models in PA. Costs and consequences of PA, and benefits due to treatment, can accrue over the lifetime of the patient. Therefore, given NICE guidelines, lifetime is appropriate[116]
Age of patients at model entry	10 years	Mean age in the PALISADE trial
Model approach	Health-state based Markov model	There is no evidence to suggest that the previous severity of an allergic reaction predicts the future severity of an allergic reaction, as verified by clinical experts.[17] Furthermore, a Markov model is most suitable for the chronic nature of the disease.
Health states (Differential tolerance; base case)	Treatment up-dosing Treatment maintenance Tolerated peanut protein of <300 mg Tolerated peanut protein of 300 mg Tolerated peanut protein of 600 mg Tolerated peanut protein of 1000 mg Tolerated peanut protein of 2000 mg	Based on the structure of the PALISADE and ARTEMIS studies and the primary outcomes reported in both (see Sections B.2.6.1 and B.2.6.3). Published literature and expert opinion supported that the important costs and consequences of peanut allergy can be captured by sensitivity to peanut protein.

	Regular inclusion of peanut in diet Spontaneous tolerance Death	
Cost categories	Treatment costs Administration costs Health state costs Adverse event costs Reaction to accidental exposure to peanut costs	Based on economic SLR and standard methodology
Source of costs	NHS reference costs, expert opinion	Standard methodology
Source of utilities	Utility survey among UK peanut allergic patients and their carers	*De novo* exercise – see Section B.3.4.4 (data on file)
Outputs	Costs, QALYs and LYs: Total Disaggregated/ aggregated	Standard methodology
Sensitivity analysis	OWSA Scenario analysis PSA	Standard methodology

EMA: European Medicines Agency; LYs: life-years; NHS: National Health Services; NICE: National Institute for Health and Care Excellence; OWSA: one-way sensitivity analysis; PA: peanut allergy; PSS: Personal Social Services; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; SLR: systematic literature review.

3.2.2 Patient population

The economic evaluation considers children and adolescents (aged 4–17 years) with a confirmed diagnosis of peanut allergy in line with the licensed indication for Palforzia and in line with the population described in the decision problem (Section B.1).[1] Treatment with Palforzia may be continued in patients 18 years of age and older (Table 27).

3.2.3 Perspective

The model adopts a National Health Service (NHS) and Personal Social Services (PSS) cost perspective (Table 27). This is in line with NICE requirements.[116]

3.2.4 Intervention

Palforzia (AR101, Aimmune Therapeutics, a Nestle Health Science Company) is the first licensed medicinal product for peanut allergy. It is an oral immunotherapy specifically designed to reduce the frequency and severity of allergic reactions to peanut by desensitising peanut-allergic children to peanut allergen.

Palforzia is indicated for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older. Palforzia should be used in conjunction with a peanut-avoidant diet (Table 27). (SmPC – see Appendix C)[1]

Palforzia should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases. Initial dose escalation and the first dose of each new up-dosing level should be administered in a health care setting prepared to manage potential severe allergic reactions.

Information on the detailed administration scheme is provided in Section 1.1.

Duration of treatment

Currently two years of clinical efficacy data are available to inform the duration of treatment with Palforzia, although Aimmune continues to assess this in the ongoing ARC008 open-label extension study.

The UK SmPC states that, efficacy data currently are available for up to 24 months of treatment with Palforzia. No recommendation can be made about the duration of treatment beyond 24 months. The effect of stopping treatment on maintenance of clinical efficacy has not been evaluated in the Palforzia clinical trial programme (SmPC – see Appendix C).[1]

It should be noted that the licensed duration of treatment for environmental allergen immunotherapies is 3–5 years.[117-119]

However, in a recent exercise to elicit UK expert opinion on long-term outcomes of Palforzia treatment for modelling purposes using the SHELF elicitation method, experts advised that in UK clinical practice most patients would likely transition to regular intake of peanut in their diet instead of Palforzia treatment after [redacted] years of therapy (see Appendix N).[120]

In the model, Palforzia in combination with avoidance is included (name used in the cost-effectiveness model: 'Palforzia'). Assumptions regarding duration of treatment are described in Section B.3.3.6.

3.2.5 Comparators

Currently, the standard of care for managing peanut allergy is limited to strict avoidance, treatment of allergic reactions in the case of exposure to peanut, and patient and caregiver education to understand and manage symptoms.

A systematic literature review of RCTs in peanut allergy identified several alternative unlicensed treatments compared to Palforzia, including other forms of unlicensed OIT, epicutaneous Viaskin-Peanut and sublingual immunotherapies (SLITs).

OIT is available in some countries to a limited extent, although in most cases funding is out-of-pocket from the patient and not paid for by the insurer or healthcare system, respectively. As such, OIT is not a relevant comparator in the UK setting.

Both SLIT and Viaskin-Peanut are investigational, not commonly used and not licensed compounds and therefore are not included as comparators in the model.

In line with the scope and decision problem, strict avoidance of peanuts (together with symptomatic treatments if exposure occurs) is the only other indicated strategy currently available in peanut allergy and is therefore included in the model as the only relevant comparator to Palforzia (referred to as “avoidance only” in the cost-effectiveness model; Table 27 and Table 28).

Table 28: Summary of the comparators

Comparators	Included/Excluded in the model	Justification/Comments
Strict avoidance of peanuts (with symptomatic treatments and emergency medication)	Included	Standard of care for management peanut allergy
Other OITs	Excluded	Not licensed in the UK, out-of-pocket, not commonly used
SLITs	Excluded	Investigational, not commonly used and not licensed in the UK
Viaskin-Peanut	Excluded	Investigational, not commonly used and not licensed in the UK

OIT: oral immunotherapy; SLIT: sublingual immunotherapy.

3.2.6 Time Horizon

The time horizon for estimating clinical and cost-effectiveness needs to be sufficiently long to reflect any differences in costs or outcomes between the medicines being compared.[116] Clinical efficacy data from the key Palforzia trials (PALISADE and

ARTEMIS) are available for up to 12 months. However, the costs and outcomes of desensitising patients can last a lifetime, as the risk of exposure exists while the patient has peanut allergy, which can be as long as the patient lives.

ICER-US recently performed a cost-effectiveness assessment of treatments for peanut allergy using a lifetime time horizon[69] whilst earlier cost-effectiveness studies identified by the SLR, used a 20-year time horizon.

Therefore, to explore all potential differences in costs and outcomes, a lifetime horizon was used in the cost effectiveness model for the base case (Table 27). The impact of alternative time horizons was tested through scenario analyses.

3.2.7 Discounting

Costs and outcomes are discounted at 3.5% per year in line with the NICE reference case (Table 27).[116]

3.2.8 Model structure

The cost-effectiveness model was developed in Microsoft Excel® using a Markov model structure (Table 27).

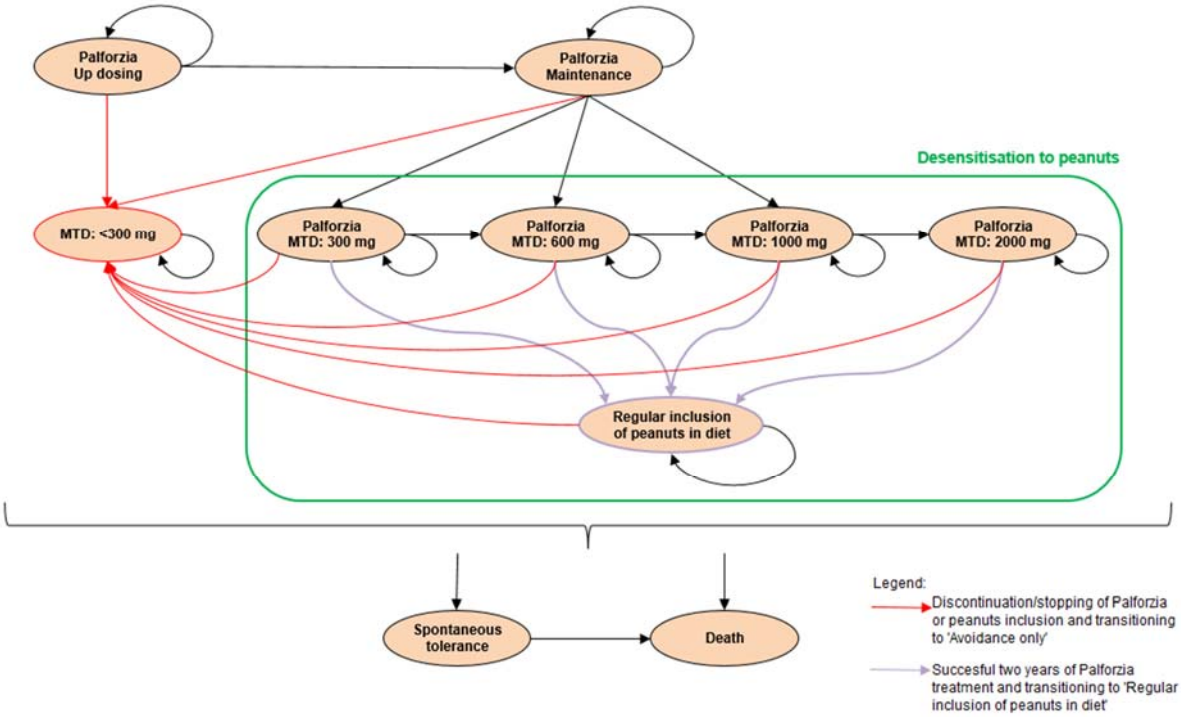
The structure of the model has been chosen based on identified models for peanut allergy,[104,106,107,109,115] which all used the Markov model structure. It has been reviewed by both clinical and health economic experts. [Personal communication with clinical and health economic experts]

The model structure separates out costs and outcomes according to different levels of desensitisation to peanut protein. The structure of the model is similar to the model presented in the ICER-US report, however instead of one health state 'peanut desensitised', several health states were included to capture differences in adverse event rates, reactions to accidental exposure to peanuts and utilities between different peanut tolerance levels.

The model structure was developed to demonstrate the significant clinical benefit and improvement in quality of life that arises from successful desensitisation following Palforzia treatment, with model health states reflecting the individual's progression through the course of treatment.

A diagram of the model structure is displayed in Figure 24 (Palforzia in combination with avoidance) and Figure 25 (avoidance only).

Figure 24: Model structure - Palforzia in combination with avoidance



MTD: maximum tolerated dose of peanut protein.

Figure 25: Model structure – avoidance only

MTD: maximum tolerated dose of peanut protein.

Patients enter the model in the 'Up-dosing' health state. After successful completion of this phase, they transition to the 'Treatment maintenance' health state. At the end of being in 'Treatment maintenance', patients have an exit food challenge to confirm their maximum tolerated dose of peanut protein and can transition to the following health states (aligned with outcomes in the PALISADE and ARTEMIS trials):

- Tolerated dose of peanut protein <300 mg, (i.e. treatment failure, patients in this health state revert to avoidance of peanuts only),
- Tolerated dose of peanut protein 300 mg,
- Tolerated dose of peanut protein 600 mg,
- Tolerated dose of peanut protein 1,000 mg,
- In the extension cycle, patients can transition again between the above dose levels tolerated and also the following health state (aligned with outcomes of the PALISADE follow-on (ARC004) study: Tolerated dose of peanut protein 2,000 mg.

Once patients complete the treatment maintenance phase, it is assumed that their level of desensitisation to peanut protein may change over time, therefore they can move between different levels of tolerance to peanut protein. Palforzia patients with a tolerated dose of ≥300 mg of peanut protein are eligible to remain on treatment in ARC004 (see Section B.2.3.3). In the model, if they remain on treatment after maintenance phase their desensitisation to peanut protein may increase, as demonstrated in ARC004. If patients stop taking Palforzia due to AEs or lack of response, or indeed they fail to complete treatment up-dosing or maintenance, it is assumed that they will revert to peanut avoidance only and their sensitivity to peanut protein will return to pre-treatment levels, which is a tolerated dose of <300 mg of peanut protein.

In the model, for patients on avoidance only, it is assumed that they will remain at the level of sensitivity observed in the exit food challenge for the remainder of the model.

The level of sensitivity to peanut protein determines the frequency of AEs and reactions to accidental exposure to peanut, as well as patient and carer utility/ disutility impact.

Patients who successfully received Palforzia treatment for 2 years can then:

- Continue Palforzia treatment and stay in the achieved level of sensitivity to peanuts (with no improvement of the desensitisation after 2 years of treatment),
- Stop treatment and transition to regular inclusion of peanut in diet to maintain desensitisation ('Regular inclusion of peanut in diet' health state),

Patients who transition to regular inclusion of peanut in diet may stay in this health state until end of life or go back to peanut avoidance only. It was assumed that their sensitivity to peanut protein will return to pre-treatment levels, which is a tolerated dose of <300 mg of peanut protein.[64]

All patients are additionally subject to the random chance of natural death and spontaneously becoming desensitised to peanut protein.

3.2.9 Transition probabilities

The following transitions between health states were included:

Transitions from the 'Up-dosing' health state

Patients enter the model in the 'Up-dosing' health state, commencing initial dose escalation (IDE) at baseline. After IDE, which is assumed to last for one day, patients either discontinue treatment and transition to 'Tolerated dose of peanut protein <300 mg', or they remain in the up-dosing health state. Thereafter, cycles within the 'Up-dosing' phase of the model are assumed to last two weeks, representing the frequency at which patients attend up-dosing visits. Patients who successfully complete escalation of treatment will remain in the 'Treatment up-dosing' health state for 20 to 40 weeks.

For the remainder of time in the treatment up-dosing phase, patients can transition to either 'Treatment maintenance', for patients who successfully complete escalation of treatment, or 'Tolerated dose of peanut protein <300 mg', for patients who do not successfully complete treatment escalation and therefore discontinue treatment. The data informing the transition rates were obtained from patient-level data (PLD) from the PALISADE study.

Transitions from the 'Treatment maintenance' health state

Patients remain in the 'Treatment maintenance' health state until they either discontinue treatment or successfully complete the PALISADE study and have a food challenge. The food challenge occurs approximately 24 weeks after entering maintenance dosing phase.

Patients who discontinue treatment transition into the 'Tolerated dose of peanut protein <300 mg' health state. Patients who successfully complete treatment maintenance and take a food challenge transition into the health state representing their maximum tolerated dose (MTD): either 'Tolerated dose of peanut protein <300 mg'; or 'Tolerated dose of peanut protein 300 mg'; or 'Tolerated dose of peanut protein 600 mg'; or 'Tolerated dose of peanut protein 1,000 mg'. The data informing the transition rates were obtained from PLD from the PALISADE trial.

Transitions from the 'Tolerated dose of peanut protein <300 mg' health state

Once patients transition to the 'Tolerated dose of peanut protein <300 mg' health state, they remain there for the remainder of the time horizon unless they experience spontaneous tolerance, at which point they transition to the 'Spontaneous tolerance' health state.

Since patients within this health state do not receive treatment, they do not get the opportunity to improve their tolerance to peanut protein and therefore cannot move to a health state with higher tolerance to peanut protein.

Transitions from the 'Tolerated dose of peanut protein 300 mg', 'Tolerated dose of peanut protein 600 mg' and 'Tolerate dose of peanut protein 1,000 mg' health states

Once patients have completed the study and taken their food challenge, patients may continue to improve or worsen their tolerance to peanut protein through continued treatment. Therefore, they may transition to either: 'Tolerated dose of peanut protein <300 mg'; 'Tolerated dose of peanut protein 300 mg'; 'Tolerated dose of peanut protein 600 mg'; 'Tolerated dose of peanut protein 1,000 mg'; or 'Tolerated dose of peanut protein 2,000 mg'. The data informing the transition rates was obtained from PLD from the ARC004 study, the follow-up study of PALISADE, whereby patients have another food challenge after a further 28 weeks or 56 weeks of treatment. It is assumed that

this transition can happen only once, in the cycle following PALISADE completion of all patients (which occurs at Week 72).

Patients within these health states may also transition to the 'Spontaneous tolerance' health state if they experience spontaneous tolerance. This transition is assumed to be possible only after the completion of the PALISADE study time horizon.

Transitions from the 'Tolerated dose of peanut protein 2,000 mg' health state

Once patients enter this health state, they are assumed to remain within it unless they discontinue treatment, where they then transition to the 'Tolerated dose of peanut protein <300 mg' health state, or experience spontaneous tolerance, where they then transition to the 'Spontaneous tolerance' health state.

Transition to 'Regular inclusion of peanut in diet'

Patients who completed two years of Palforzia may stop the treatment and start to include peanuts in their diet ('Regular inclusion of peanut in diet' health state).

Transition from 'Regular inclusion of peanut in diet'

Patients who transition to 'Regular inclusion of peanut in diet' after successful completion of two years of Palforzia may stay in that health state until end of life or discontinue and go back to avoidance only with a tolerated dose of <300 mg of peanut protein.

Transitions to 'Spontaneous tolerance'

After the completion of the PALISADE study time horizon, patients may transition to the 'Spontaneous tolerance' health state if they experience spontaneous tolerance.

Transitions to 'Death'

All patients are additionally subject to the random chance of natural death at any time period. No mortality impact of treatment is assumed in the model base case.

3.2.10 Cycle length

The length of cycles was variable to capture the follow-up periods in the Palforzia trials: PALISADE (base case) and ARTEMIS (sensitivity analyses). Therefore, 1 day for the first cycle (during IDE within 'Up-dosing' health state, based on the Palforzia UK SMPC[1]), then every 2 weeks for up-dosing until a maximum maintenance dose of 300

mg is achieved, which required an average of 22 weeks in total and a maximum of 20 cycles or 40 weeks in PALISADE (see Section B.2.3). Thereafter, the cycle length is 4 weeks (during the subsequent visits of the maintenance phase). There is one 'extension' cycle, which has a cycle length that completes the year following maintenance. Following the extension cycle, in the extrapolation phase, every cycle length is annual. The lengths of cycles, and number of cycles, used in the model are presented in Table 29.

Table 29: Cycle length by phase

Model phase	Number of cycles in the base case (PALISADE)	Cycle duration (days)
IDE	1	1.00
Up-dosing	20	14.00
Maintenance	8	28.00
Extension	1	224.50
Extrapolation	88	365.25

These cycle lengths are in line with the frequency of contact during the PALISADE study. The cycles are also intended to be short enough to capture differences in the incidence of TRAEs which may be higher during IDE and up-dosing than in later stages of treatment. Additionally, this cycle length precisely captures the occurrence of discontinuation, which is a key driver of the accumulation of costs for Palforzia, particularly during up-dosing. The number of cycles in the base case is set up such that each patient experiences a maximum 21 cycles of up-dosing and 8 cycles of maintenance before moving into 1-year cycles for the remainder of their lifetime. Patients can finalise each phase of administration of Palforzia faster and then transition to relevant health states earlier than after 21 model cycles but the cycle duration is fixed e.g. many patients will enter the maintenance health state still during the 14 day cycle up-dosing phase of the model.

The number of cycles the model uses can be varied by the user with up to 32 cycles of data specified; the user can specify the duration of the initial dose escalation, up-dosing, maintenance, and extrapolation cycles.

B.3.3 Clinical parameters and variables

The results of the pivotal trials, PALISADE and ARTEMIS comparing Palforzia versus placebo, were used to inform the clinical parameters for Palforzia and avoidance.[121] (See Section B.2.2) Data from the follow-on of the PALISADE trial (ARC004) were also utilised to project the extrapolation of treatment with Palforzia.[65]

As discussed in the meta-analysis section (see Section B.2.8), efficacy data from the PALISADE[39] and ARTEMIS[76] studies were not integrated due to differences in study eligibility requirements and study duration.

As a result, cost effectiveness is considered independently for each study.

Within the model, the base case analysis uses the PALISADE trial (together with ARC004 follow-on) whilst the ARTEMIS data are utilised within a sensitivity analysis (also together with ARC004 follow-on). The rationale for utilising PALISADE as the base case is to ensure that the largest, most robust data set is used on which to base recommendations (496 patients aged 4-17 in PALISADE compared with 175 patients in ARTEMIS). Additionally, the PALISADE trial has longer-term data available (approximately 2 years' Palforzia efficacy data are available for PALISADE and ARC004 follow-on, compared to approximately 9 months for ARTEMIS).

From year 1 onwards, given low patient numbers by health state in ARC004 coupled with sparsity of events, a separate risk reduction model based on analysis of PALISADE was used to estimate the reduction in reactions due to accidental exposure to peanut.[122] This model was also used to estimate occurrence of accidental exposures to peanuts for patients with a tolerated dose of peanut protein <300 mg.

Base case inputs from PALISADE are described in the sections below (see Table 30 to Table 43 below), inputs from ARTEMIS, used in sensitivity and scenario analysis, are presented in the Appendix O.

Detailed description of the PALISADE trial design is provided in the clinical effectiveness sections (see Sections B.2.3 and B.2.4).

Clinical parameters within the model have been categorised into inputs relating to treatment efficacy (maximum level of peanut protein that can be tolerated, frequency of reactions to accidental exposure to peanut), treatment discontinuation/stopping and

adverse events. When the main publication or clinical study report did not report results for the ITT population in sufficient granularity, post-hoc analysis of the patient-level data were conducted to source clinical inputs for these events. In the absence of data, probabilities for the remaining events were sourced from assumption, validated by clinical expert opinion.

In the base case the trial data were used to inform:

- Baseline demographics,
- Probabilities of tolerating a dose of peanut protein of <300 mg, 300 mg, 600 mg, or 1,000 mg after 12 months of treatment (exit of PALISADE),
- Probability of changing tolerated dose of peanut protein from 300 mg, 600 mg, or 1,000 mg to <300 mg, 300 mg, 600 mg, 1,000 mg or 2,000 mg (exit of ARC004),
- Discontinuation and compliance rates (PALISADE and ARC004),
- Reactions to accidental exposures to peanut protein which required treatment with or without adrenaline (PALISADE + extrapolation based on a Risk Quantification Study (see Section 3.3.3 for detailed description of the study),
- Mild and moderate treatment-related anaphylactic reactions as a result of treatment (PALISADE, ARC004),
    - Severe anaphylaxis was rare (one case reported in PALISADE, two cases in ARC004 daily dosing cohorts but later corrected to one,[67] no cases in ARTEMIS) hence severe anaphylaxis was not included in the model.
- Moderate treatment related adverse events (TRAEs) occurring in at least 5% of one study arm (PALISADE, ARC004).
    - Mild TRAEs were assumed to drive minimal cost and disutility impact hence were excluded.
    - Severe TRAEs were very rare with frequency below 5% hence were excluded.

In addition, the effect of discontinuing active treatment was added in the model based on data obtained in the SHELF expert elicitation exercise.[120] (see Section 3.3.6 and Appendix N). Findings from literature confirmed by expert opinion were used to estimate probability of spontaneous tolerance. Furthermore, life tables for the UK were used to inform the probability of death due to other causes than peanut allergy.[123]

3.3.1 Baseline demographics

To align the model with the main sources of clinical data, patient demographics at baseline were based on the intention-to-treat (ITT) population of the PALISADE trial, as shown in Table 30.

Table 30: Baseline demographics of ITT cohort entering the model in PALISADE trial

Parameter at baseline	Base case
Mean age (years)	10
Sex, n (%)	
Male	284 (57.3%)
Female	212 (42.7%)
Baseline specific peanut allergy characteristics	
Peanut-specific IgE, median (kUA/L)	[redacted]
Maximum tolerated dose (mg) n (%)	
None	[redacted]
1 mg	[redacted]
3 mg	[redacted]
10 mg	[redacted]
30 mg	[redacted]
Skin prick test mean wheal diameter, median (mm)	[redacted]
History of asthma, n (%)	[redacted]

IgE: immunoglobulin E; ITT: intention-to-treat; n: number.
Source: Vickery et al., 2018;[75] ARC003 Clinical study report[39]

3.3.2 Treatment efficacy – Tolerated level of peanut protein

The efficacy of Palforzia is measured as the maximum level of peanut protein that can be tolerated by ingestion. This was measured in the clinical setting by patients undertaking a DBPCFC following completion of the treatment escalation and maintenance phases of PALISADE and a further DBPCFC at exit of ARC004. The possible maximum levels of tolerance to peanut protein were: <300 mg, 300 mg, 600 mg, 1000 mg and 2000 mg. Patients were assigned to the health state representing the maximum dose of peanut protein tolerated on study exit.

In the model, treatment efficacy is captured by the probability of attaining different maximum tolerated doses of peanut protein and thus assigned health states. The possible transitions between health states within the model are described in Section B.3.2.8. The transition matrices used in the model were derived from PLD of PALISADE and ARC004.

At the end of Week 72, i.e. after all PALISADE patients have exited the study and after all transition matrices are applied for the PALISADE PLD analysis, [redacted] of 'avoidance only' patients are in the tolerated dose of peanut protein <300 mg health state. Only [redacted] of 'avoidance only' patients reside in the tolerated dose of peanut protein ≥300 mg health state. This is aligned with the published results of the PALISADE study,[38] whereby 8.1% of placebo patients achieved a tolerated dose of peanut protein ≥300 mg in the exit DBPCFC.

Similarly, from the PLD at the end of Week 72, [redacted] of Palforzia patients were in the tolerated dose of peanut protein <300 mg health state, and [redacted] patients were in a tolerated dose of peanut protein ≥300 mg health state. Again, this is aligned with the published results whereby 76.6% of Palforzia patients tolerated ≥300 mg of peanut protein during their exit DBPCFC. Additionally, from the PLD analysis [redacted] Palforzia patients were in the tolerated dose of peanut protein 1,000 mg health state, closely aligned with 50.3% of Palforzia patients achieving a tolerated dose of peanut protein of 1,000 mg in the exit DBPCFC in the PALISADE study.

A summary of the final patient distributions following completion of the RCT phase of PALISADE is given in Table 31.

Table 31: Week 72 patient distribution from PALISADE trial for avoidance and Palforzia

	Treatment escalation	Treatment maintenance	Tolerated dose of peanut protein <300 mg	Tolerated dose of peanut protein 300 mg	Tolerated dose of peanut protein 600 mg	Tolerated dose of peanut protein 1000 mg	Tolerated dose of peanut protein 2000 mg	Spontaneous tolerance
Avoidance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palforzia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC003 PLD data on file

Table 32 presents the transition matrix that is applied once all Palforzia patients have completed maintenance (Week 72 for PALISADE) demonstrating continued benefit of Palforzia treatment, based on analysis of the PALISADE follow-on study ARC004 patient level data (Cohorts 1 and 3A). This matrix is applied in the extension cycle up to 2 years of treatment.

The patient distribution following the application of the ARC004 transition matrix to PALISADE patients is presented in Table 32.

Table 32: ARC004 transition matrix (n=129 patients completing ARC004 Cohorts 1 and 3A)

Number of patients	Treatment escalation	Treatment maintenance	Tolerated dose of peanut protein <300 mg	Tolerated dose of peanut protein 300 mg	Tolerated dose of peanut protein 600 mg	Tolerated dose of peanut protein 1000 mg	Tolerated dose of peanut protein 2000 mg	Spontaneous tolerance
Treatment escalation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein <300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 1000 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 2000 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous tolerance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Summary								
Total number of patients in a heath state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of patients in a health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC004 PLD data on file
Analysis is based on patients who fully completed ARC004 study procedures including the exit DBPCFC: Cohort 1 n=103; Cohort 3a n=26, sum total n=129.

The transition matrix aligns with the outcomes reported in the longer-term safety and efficacy submitted manuscript for the PALISADE and ARC004 studies, as follows.[67]

- In the transition matrix [redacted] of patients transition to the tolerated dose of peanut protein of <300 mg health state during the course of the study ARC004. This is aligned with the PALISADE and ARC004 manuscript which reported that 1.9% of patients of Group A (Cohort 1, total population: 104 patients, ~1.5 years of

treatment) and 0% of patients of Group B (Cohort 3A, 26 pts total, ~2 years of treatment) did not achieved a tolerated dose of peanut protein ≥300 mg at ARC004 exit.[67] (Note that the PALISADE and ARC004 manuscript refers to the ARC004 "completer population" for cohort 1 as n=104, whereas the model assumes n=103. This is due to one study participant only partially completing the exit DBPCFC hence they were excluded.)

- In the transition matrix [redacted] of patients transition to the tolerated dose of peanut protein of 300 mg health state, which is aligned with the 8.7% of patients in Group A (Cohort 1) and 3.8% of patients in Group B (Cohort 3A) with a tolerated dose of peanut protein of 300 mg at exit of ARC004 reported in the PALISADE and ARC004 long-term manuscript.[67]
- [redacted] of the patients transition to the tolerated dose of peanut protein of 600 mg health state, which is also aligned with 9.6% of patients in Group A and 0% in group B with a tolerated dose of peanut protein of 600 mg.[67]
- [redacted] of patients transition to a tolerated dose of peanut protein 1000 mg, which aligns with 31.7% of patients in Group A and 15.4% in Group B with a tolerated dose of peanut protein of 1000 mg.[67]
- [redacted] of patients tolerated a dose of peanut protein of 2000 mg, aligned with the 48.1% of patients in Group A and 80.8% in Group B achieving the same tolerated dose of peanut protein at exit DBPCFC in the ARC004 study.[67]

3.3.3 Treatment efficacy – Reactions to accidental exposure to peanut protein

Reactions to accidental exposures to peanut protein that required treatment are considered in the model regardless of their frequency as another efficacy outcome in addition to the desensitisation outcomes. It is also identified which of these reactions required treatment with adrenaline as this affects associated costs.

The occurrence of accidental exposures to peanut protein was taken from PALISADE for year 1 of the model, for patients who are in up-dosing and maintenance. From year 1 onwards, given low patient numbers by health state in ARC004 coupled with sparsity of events, a separate risk reduction model based on analysis of PALISADE was used to estimate the reduction in reactions due to accidental exposure to peanut. This model

was also used to estimate occurrence of accidental exposures to peanuts for patients with a tolerated dose of peanut protein <300 mg.

Careful consideration was given to avoid double counting of anaphylactic reactions, as such and as reactions due to accidental peanut exposure. The anaphylactic reactions presented in the AE analysis are treatment-related, not due to accidental peanut exposure (see Section B.2.10.2).

The accidental peanut exposures that required treatment were considered irrespective of any anaphylactic reaction which may or may not have occurred and were considered collectively regardless of severity of reaction.

Reactions to accidental exposure to peanut occurring during the PALISADE study

The information for the rates of reactions during PALISADE are informed by a poster presented at the American Academy of Allergy, Asthma & Immunology 2019 Annual Meeting.[124] The poster gives the rate of accidental exposures that required treatment during up-dosing and maintenance. Only accidental exposure reactions requiring treatment are included in the model, as accidental exposures not requiring treatment would be assumed to have no cost or QALY impact. The number of events that required adrenaline as a treatment over the whole study are additionally presented.

Reactions were stratified into two mutually exclusive categories:

- Reactions to accidental exposure to peanut that require treatment with adrenaline – estimated as those events that required treatment in each phase multiplied by the proportion of those that required adrenaline over the whole cycle.
- Reactions to accidental exposure to peanut that require treatment but not require adrenaline – calculated as those reactions that required treatment minus those that required adrenaline.

The number of reactions in the up-dosing, maintenance and overall are presented in Table 33.

Table 33: Occurrence of reactions to accidental exposures to peanut requiring treatment in PALISADE (number of patients experiencing at least 1 accidental exposure)

Adverse reactions	Up-dosing		Maintenance		Overall	
	Palforzia (N=366)	Placebo (N=123)	Palforzia (N=310)	Placebo (N=118)	Palforzia (n=372)	Placebo (n=124)
Reactions requiring treatment	19	8	5	6	24	13
Reactions requiring adrenaline	0	---	0	---	0	3
Reactions requiring treatment, not adrenaline	19	---	5	---	24	10

--- not reported in the poster

Note: Patients may have reported more than 1 accidental exposure.

Source: Poster presented at the American Academy of Allergy, Asthma & Immunology 2019 Annual Meeting.[117]

During the PALISADE trial, none of the accidental exposures required adrenaline. In the placebo arm 23% (3 out of 13) of reactions that required treatment required adrenaline in the overall population.[124] This proportion was applied to up-dosing and maintenance in the placebo arm to stratify reactions by adrenaline use.

The rates of the reactions that occurred over the study periods are converted into per-cycle probabilities using Equation 1 from Briggs et al. (2006).[125] In this formula, r indicates a rate, t is the time of interest (number of cycles within the phase of the model). It was assumed that in the PALISADE trial mean duration of up-dosing phase was 22 weeks, maintenance duration was 25 weeks, mean total duration was 44 weeks.[39]

Equation 1: Briggs et al. (2006) formula for conversion of per-cycle probabilities

$$p = 1 - e^{-\frac{r}{t}}$$

The per-cycle probabilities are applied in the model each cycle (presented in Table 34).

Table 34: Probabilities of adverse reactions to accidental exposures to peanut protein applied per cycle

Reactions	Up-dosing		Maintenance	
	Palforzia (N=366)	Placebo (N=123)	Palforzia (N=310)	Placebo (N=118)
Reactions requiring treatment	0.47%	0.59%	0.26%	0.81%
Reactions requiring treatment with adrenaline	0%	0.14%*	0%	0.19%*
Reactions requiring treatment not with adrenaline**	0.47%	0.45%	0.26%	0.62%

*Calculated as 23% of all reactions requiring treatment

**Calculated as those reactions that required treatment minus those that required adrenaline

Extrapolated reactions to accidental exposure to peanut

Aimmune Therapeutics performed a risk quantification study to estimate the risk of adverse reactions to accidental exposure to peanut protein before and after Palforzia treatment, using PALISADE data.[122] The outputs of this analysis are used in the model.

In Stage 1 of the study, PALISADE baseline data and patient history were used to estimate the daily risk of peanut protein exposure in milligrams (mg) and the daily risk of anaphylactic reactions before Palforzia treatment. (Note that anaphylactic reactions were described as systemic allergic reactions in the study.) Baseline questionnaire data on the number of prior anaphylactic reactions over each patient's lifetime was used to estimate the likelihood of accidental exposure. A maximum value for the daily accidental exposure of 1500 mg (approximately five to six peanut kernels) was assumed considering that patients with peanut allergy would attempt to avoid peanuts and that accidental exposure is usually due to a limited amount of peanut exposure.

Maximum tolerated dose (MTD) levels collected via the DBPCFC conducted at PALISADE screening were used to estimate minimal eliciting dose (MED) for each patient pre-treatment, i.e. the lowest dose triggering a reaction (see Section B.2.3.1). A patient's MED was assumed to be one incremental dosage level higher than their MTD during the DBPCFC e.g., a patient's MED would be set to 10 mg if their prior dose of 3 mg was determined to be the MTD.

Based on the estimated peanut protein exposure distribution in Stage 1 and estimated MED levels at the screening DBPCFC, the daily absolute risk of anaphylactic reactions

before Palforzia treatment was calculated and further converted to the risk over a one-year period assuming a parametric distribution, as summarised in Table 35.

Table 35: Mean annual risk of exposure

Parametric distribution	Annual risk
Weibull	[redacted]
Lognormal	[redacted]
Loglogistic	[redacted]

Source: Risk quantification study[122]

Value [redacted] (lognormal distribution) was used as a baseline annual risk of accidental exposures that would require treatment (adjusted by formula (1)). This value was applied to patients who can tolerate < 300mg of peanut protein.

In stage 2 of the study, the same analysis to calculate the risk of anaphylactic reactions was performed using the MED levels observed in the exit DBPCFC of PALISADE following desensitisation to peanut. Comparison between the estimates for the distributions for the daily incidence of reaction at the trial's beginning and end gives a measure of the change in risk associated with a change in tolerance of peanut protein. The resulting risk reductions according to parametric distribution are reported in Table 36.

Table 36: Risk reduction according to maximum tolerated dose (MTD), minimum eliciting dose (MED) and distribution

MTD at exit (mg)	Estimated MED at exit (mg)	Mean relative risk reduction		
		Weibull	Lognormal	Loglogistic
300	600	[redacted]	[redacted]	[redacted]
600	1,000	[redacted]	[redacted]	[redacted]
1,000	1,000			

MED: minimum eliciting dose.
Source: Risk quantification study[122]

For patients whose MTD was 1,000 mg, i.e. the highest dose level at exit DBPCFC, MED was not available and was conservatively assumed to be 1,000 mg.

The outputs of the analysis were time adjusted to annual probabilities using Equation 1 for use in the model and are presented in Table 37. The middle value parametric distribution (Lognormal) was chosen for frequency of reactions (both before and after treatment), providing a conservative estimate compared to published rates for the

annual incidence of reactions (e.g. Cherkaoui et al., 2015,[43] estimates an annual incidence rate of 12.4%). The estimated risk reduction level due to treatment is also in line with other estimates in the literature (e.g. the ICER-US model estimates a 95% reduction in moderate-to-severe reactions[104] and Baumert et al., 2018,[126] estimates this rate at greater than 95%). Additionally, it is assumed that patients tolerating 2,000 mg of peanut protein will experience the same probability of reaction as those tolerating 1,000 mg due to the data for the 2,000 mg tolerability level not being available in the PALISADE study. Furthermore, the proportion of events requiring treatment with adrenaline was taken from the PALISADE study as well, with 3 of 37 reactions requiring treatment with adrenaline amongst both Palforzia and placebo patients. For patients who switch to regular inclusion of peanut in diet, probability of reactions as for 2,000 mg MTD was used.

Table 37: Combined weighted average for annual reactions probabilities for the extension study applied in the model

Accidental exposures to peanuts	Probability of adverse event per year by MTD				
	<300 mg	300 mg	600 mg	1000 mg	2000 mg
Requiring treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring treatment but not with adrenaline*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring treatment with adrenaline**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MTD: maximum tolerated dose.

*Calculated as those reactions that required treatment minus those that required adrenaline

*Calculated as 8.1% (3 of 37) all reactions requiring treatment

Source: Risk quantification study[122]

3.3.4 Safety data: Treatment-related adverse events (TRAEs), including anaphylactic reactions

It has been shown that the longer patients remain on treatment with Palforzia, the fewer TRAEs they experience.[77] It was also demonstrated that severity of symptoms decreases over time.[77] Therefore, the rates of TRAEs were captured separately for up-dosing, maintenance and thereafter. Data on TRAEs were collected according to health state from PALISADE and ARC004 to demonstrate safety following the RCT study-phase. TRAEs in the model are split into anaphylactic reactions, and other non-anaphylactic TRAEs.

Only TRAEs occurring in peanut allergy patients aged between 4 and 17 (the licensed population) were considered for inclusion in the model.

AEs that occurred in either DBPCFC were not considered to be a result of the effect of Palforzia nor avoidance and are therefore not considered within the model.

Treatment-related anaphylactic reactions

Severe anaphylaxis was rare (one case reported in PALISADE, two cases in ARC004 daily dosing cohorts but later corrected to [redacted],[67] no cases in ARTEMIS) hence was not included in the model.

All cases of mild and moderate systemic anaphylactic reactions related to Palforzia were included in the model.

It was assumed that all patients on avoidance (all health states) and patients in the Palforzia arm who discontinued the treatment and switched to avoidance did not experience treatment-related anaphylactic reaction.

Treatment-related anaphylactic reactions during PALISADE trial

The number of mild and moderate treatment-related anaphylactic reaction during Palforzia up-dosing and maintenance were extracted from the PALISADE trial (Table 38) and converted to rates per cycle (Table 39).

Table 38: Treatment-related anaphylactic reactions in the PALISADE study

Adverse event	Treatment up-dosing		Maintenance	
	Palforzia (N=366) n (%)	Avoidance only (N=123) n (%)	Palforzia (N=310) n (%)	Avoidance only (N=118) n (%)
Mild treatment-related anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]
Moderate treatment-related anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC003 Clinical study report[39]

Table 39: Anaphylactic reactions probabilities per cycle for patients during the PALISADE study

Adverse event	Treatment up-dosing		Maintenance	
	Palforzia	Avoidance only	Palforzia	Avoidance only
Mild anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC003 Clinical study report[39]

Treatment-related anaphylactic reactions occurring during the PALISADE follow-on study (ARC004)

PLD analysis was used in order to ascertain the treatment-related anaphylactic reaction rates by dose tolerated health states for ARC004 since the CSR did not report results in sufficient granularity. Patients aged 4 to 17 who continued treatment with 300 mg Palforzia once a day, in line with the licence for Palforzia, were considered within the analysis; these are patients within "Cohort 1" and "Cohort 3a" of the study (see Table 4 in Section 2.2).

The percentage of patients within each health state experiencing the treatment-related anaphylactic reactions for Cohorts 1 and 3a are presented in Table 40, with the adjustment to annual rates in Table 41.

The weighted average of treatment-related anaphylactic reactions is presented in

Table 42.

Table 40: Treatment-related anaphylactic reaction rates and annual probabilities for Cohort 1

Adverse event	Percentage of patients by MTD			Annual probability of event by MTD		
	300 mg (N= 16)	600 mg (N=25)	1000 mg (N=68)	300 mg	600 mg	1000 mg
Mild anaphylactic reaction Palforzia-related						
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated percentage of patients who experienced the event (including all events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reaction Palforzia-related						
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated percentage of patients who experienced the event (including all events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MTD: maximum tolerated dosed.
Source: ARC004 PLD data on file

Table 41: Treatment-related anaphylactic reaction rates and annual probabilities for Cohort 3a

Adverse event	Percentage of patients by MTD			Annual probability of event by MTD		
	300 mg (N= 1)	600 mg (N=10)	1000 mg (N=19)	300 mg	600 mg	1000 mg
Mild anaphylactic reaction Palforzia-related						
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated percentage of patients who experienced the event (including all events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reaction Palforzia-related						
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated percentage of patients who experienced the event (including all events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MTD: maximum tolerated dosed.
Source: ARC004 PLD data on file

Table 42: Combined weighted probabilities of treatment-related anaphylactic reactions in ARC004

Adverse event	Overall weighted average		
	Time adjusted annual rates by MTD		
	300 mg	600 mg	1000 mg
Mild anaphylactic reactions Palforzia-related	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reactions Palforzia-related	[redacted]	[redacted]	[redacted]

TEAE: treatment emergent adverse event; MTD: maximum tolerated dose.

There were no anaphylactic events in the health state tolerated dose of peanut protein 300 mg. Conservatively, it was assumed that in this health state rates will be similar to the rates in both up-dosing and maintenance phases combined in the PALISADE study.

In the ARC004 study there is no data to parametrise the treatment-related anaphylactic reactions in the health state tolerated dose of peanut protein 2000 mg. Therefore, the probability of experiencing an anaphylactic reaction in this health state is assumed to the same as that in 1000 mg health state. Furthermore, for regular inclusion of peanut in diet the same probability as for 1000 mg was applied. Probabilities of anaphylactic reactions included in the model are summarised in Table 43.

Table 43: Probabilities of treatment-related anaphylactic reactions included in the model

Adverse event	Probability per cycle				
	300 mg	600 mg	1000 mg	2000 mg	Regular inclusion of peanuts
Mild anaphylactic reactions Palforzia related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reactions Palforzia related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The annual treatment-related anaphylactic reaction probabilities calculated for each health state are applied each year for the remainder of the model time horizon to all patients within each health state. The probabilities calculated from ARC004 are used in the extrapolation for both the PALISADE (base case) and ARTEMIS (sensitivity analysis) studies.

Non-anaphylactic TRAEs

In the model, treatment-related non-anaphylactic AEs were summarised and included by organ system. This was in order to report TRAEs conservatively, as there were several similar but not identical TRAE symptoms (e.g. moderate throat irritation, moderate throat tightness, moderate cough) reported in the trials which, individually had lower incidence than 5% but collectively by organ system exceeded 5%. This grouping of TRAEs was possible as their resource use and QALY impact were deemed to be the same by a clinical expert.

Only mild serious, moderate, and severe treatment-related AEs that occurred in ≥5% in at least one arm of the study population of the PALISADE and ARTEMIS studies were included. Mild serious TRAEs, and moderate and severe TRAEs which did not occur in at least once in ≥5% of patients in at least one study arm were not included in the model.

While mild treatment-related serious adverse events and severe TRAEs were considered for inclusion in the model, there were insufficient numbers of patient who experienced them to justify their inclusion.

TRAEs occurring during the PALISADE study

The rates of TRAEs during PALISADE were informed by PLD.[39]

TRAEs occurring during 'Initial dose escalation (IDE)' study period were combined with up-dosing as there were few events in this short study phase. The number of events and frequency of TRAEs for 'Up-dosing including IDE' and 'Maintenance' taken from the PALISADE PLD are presented in Table 44.[39]

Table 44: Non-anaphylactic treatment-related AEs in the PALISADE study, by organ system

Adverse event	Treatment up-dosing including IDE		Maintenance	
	Palforzia (N=366) n (%)	Avoidance only (N=123) n (%)	Palforzia (N=310) n (%)	Avoidance only (N=118) n (%)
Moderate gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC003 Clinical Study Report[39]

The TRAE rates that occurred over the entirety of each study period were adjusted for cycle length and converted to probabilities using Equation 1 from Briggs et al. (2006).[125] The probabilities for TRAEs for Palforzia and avoidance patients per cycle are presented in Table 45,

Table 45: Non-anaphylactic treatment-related AEs per cycle for patients during the PALISADE study

Adverse event	Treatment up-dosing		Maintenance	
	Palforzia	Avoidance only	Palforzia	Avoidance only
Moderate gastrointestinal disorders (including moderate (upper) abdominal pain, vomiting, nausea)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]

(including moderate cough, throat irritation and tightness, sneezing, wheezing)				
Moderate skin and subcutaneous tissue disorders (including moderate pruritus, urticaria, rash)	[redacted]	[redacted]	[redacted]	[redacted]

Non-anaphylactic TRAEs occurring during the PALISADE follow-on study (ARC004)

PLD analysis was used in order to ascertain the TRAE rates by dose tolerated health states for ARC004 since the CSR did not report results for the ITT population in sufficient granularity. No moderate or severe non-anaphylactic TRAE occurred in ≥ 5% of patients during ARC004, within cohorts 1 and 3A. A total of [redacted] moderate TRAEs were reported overall occurring in a total of [redacted] patients, of which [redacted] were respiratory symptoms occurring in 5 patients (Table 46).

Table 46: Non-anaphylactic TRAEs reported in the ACR004 trial

Moderate TRAE by organ system	Cohort 1 and 3A combined	
	n patients	n events
Eye	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Total	[redacted]	[redacted]

Source: ARC004 PLD data on file

Based on the decreasing trend in TRAEs rates during up-dosing and maintenance in the PALISADE study and low frequency of TRAEs during the follow-on study (ARC004), no TRAEs were assumed after the up-dosing and maintenance phases. TRAE probabilities included in the model are presented in Table 47.

Table 47: TRAEs probabilities included in the model

Adverse event	Frequency of non-anaphylactic TRAEs					
	<300 mg	300 mg	600 mg	1000 mg	2000 mg	Regular inclusion of peanuts
Moderate treatment-related TEAEs including: Moderate gastrointestinal disorders,	0%	0%	0%	0%	0%	0%

Moderate respiratory, thoracic and mediastinal disorders, Moderate skin and subcutaneous tissue disorders						

3.3.5 Spontaneous tolerance

The data for patients transitioning to the 'Spontaneous tolerance' health state is based on the assumption that 5% of patients will transition into spontaneously tolerance over the model horizon. This was assumed for both Palforzia and avoidance alone. It was also assumed that there will be no modification in spontaneous tolerance due to treatment. This assumption was confirmed by clinical experts.[120]

3.3.6 Treatment duration (moving from Palforzia treatment to other interventions)

Discontinuation of Palforzia treatment during first 2 years of treatment was extracted from PALISADE and ARC004 trials and incorporated in transition matrixes as moving to 'Tolerated dose of peanut protein <300 mg' health state (see Section 3.3.2).

In the SHELF expert elicitation exercise, experts advised that most UK patients would likely transition to regular intake of peanut in diet after [redacted] years of therapy in UK clinical practice (see Appendix N).[120] Based on the experts' opinion the following assumptions were made:

- After [redacted] years of Palforzia treatment (i.e., at beginning of year 3) [redacted] of patients will continue Palforzia treatment until end of life (this represents patients who will not be willing to switch to regular inclusion of peanut in diet due to various reasons). These patients will stay in the MTD health state achieved at the end of 2 years.
- After [redacted] years of Palforzia treatment [redacted] of patients will stop the treatment and will transition to regular inclusion of peanut in diet. Out of these patients, during next 2 years [redacted] will drop out and revert to avoidance. The rest of patients will maintain regular inclusion of peanut in diet until end of life.

Transition probabilities for patients after [redacted] years of Palforzia treatment are summarised in Table 48 and presented in Figure 26.

Table 48: Transition probabilities for patients after 2 years of Palforzia treatment

Health state	Beginning of 3rd year	Beginning of 4th year	Beginning of 5th year	Rest of time horizon
On Palforzia – the same MTD level as at the end of 2 years	[redacted]	[redacted]	[redacted]	[redacted]
On 'Regular inclusion of peanut in diet'	[redacted]	[redacted]	[redacted]	[redacted]
On 'Avoidance only'	[redacted]	[redacted]	[redacted]	[redacted]

MTD: maximum tolerated dose.

Figure 26: Transition probabilities for patients after 2 years of Palforzia treatment

Details of the SHELF expert elicitation exercise are presented in Appendix N.

B.3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

Peanut allergy can have a significant impact on the HRQoL of people with peanut allergy, and also their caregivers and wider families. One of the key objectives of Palforzia treatment is to improve HRQoL, especially improving anxiety about severe reactions and the ability to lead a normal day to day life in terms of usual activities.

Disease-specific HRQoL was assessed in the clinical trial programme using FAQLQ and FAIM measures (see Section B.2.6.4 for results). As noted within the Clinical Effectiveness section (see Section B.2.13), measuring HRQoL in peanut allergy clinical trials presents some issues, in particular the masking effect of blinding within a clinical trial, and the delay to seeing the beneficial effects on HRQoL once unblinding occurs (i.e. the time it takes trial individuals to adjust to the benefits of their new health state once unblinding occurs). In particular, when blinded to treatment, patients and caregivers are unaware if they are protected from accidental exposures to peanut,

hence anxiety about reactions and HRQoL would not be expected to improve, unlike in a real-life treatment setting.

For these reasons, the HRQoL data collected in the pivotal clinical trials was not considered to fully capture the real-life impact of Palforzia. As such, for the purposes of informing the model a quality-of-life and utility survey independent of the clinical trials was performed (see Section 3.4.4 and Appendix P).

3.4.2 Mapping

A mapping of FAQLQ to a preference-based utility measure such as EQ-5D was considered but discounted for the same reasons as above, as any mapped EQ-5D utility values from the Palforzia trials would still be impacted by the masking issue.

Additionally, Aimmune determined that insufficient observational datasets exist which would facilitate mapping (i.e. which collected both FAQLQ and a preference based utility measure in populations generalizable to Palforzia treatment in the UK, and representative of the key health states in the model). In particular, as Palforzia is a new treatment, existing observational datasets would include few if any treated, desensitised patients, yet the critical question a mapping would need to address would be how patient utility is likely to be impacted due to desensitisation treatment. As such, Aimmune anticipated that developing a reliable mapping would be problematic.

3.4.3 Health-related quality-of-life studies

SLR searches for relevant health-related quality-of-life data are described in Appendix H.

There is limited quality of life evidence in the existing literature to inform the model (see Appendix H). A peanut allergy health related quality of life SLR found the following values for peanut or food allergy, mostly pertaining to untreated patients, i.e. those in the tolerate <300mg (peanut avoidance only) health state:

- Utility value for peanut allergy and peanut OIT of 0.92, which was derived from a utility for food allergy [0.85].[107]

- Utility values for peanut allergy stratified by severity (severity of allergy was assessed by caregivers): 0.768 for severe group, 0.863 for mild group, 0.909 for moderate group, 0.873 for total group.[54]
- Utility for food allergy ranging from 0.74–0.78.[127] Further targeted literature searches identified a number of utility values from broader food allergy which may be applied to the model including:
- Utilities for patients with and without food allergy [0.84 versus 0.94, respectively],[128]
- Utilities for patients with and without a history of anaphylaxis [0.88 versus 0.79, respectively],[128]
- Utilities for patients with and without an adrenaline injector [0.91 versus 0.78, respectively],[128]
- Disutility related to negative health state influences for food allergy: -0.09.[108,111,112,129]

It is also common for caregivers to be burdened by their dependent's peanut allergy, as there is anxiety surrounding the risks of accidental exposure to peanut. A disutility of 0.09 for parents or caregivers of children with severe allergic reaction due to food allergy has been previously reported.[130]

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Given the limited evidence in the literature in terms of patient and caregiver utilities, especially pertaining to the likely utility impact of treatment, for the purposes of informing the model, Aimmune Therapeutics conducted a quality-of-life and utility survey among UK peanut-allergic patients and their caregivers (using EQ-5D and EQ-5D-Y measures) to understand the real-life impact of Palforzia on HRQoL. In consultation with health economic experts, this approach to generating utility evidence was adopted in preference to other methods (such as a vignette study to develop peanut allergy-specific utility values) in order to adhere closely to the NICE reference case, in particular with health status reported by patients and carers and evaluated based on societal preferences, using the EQ-5D value set. Details of the utility survey are presented in the Appendix P.

Table 49: Utilities, EQ-5D - Survey: caregiver-reported child and caregiver EQ-5D (treatment-naïve; n=100)

Health state	Child		Caregiver	
	Mean	SE	Mean	SE
Current HRQoL	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]	[redacted]

HRQoL: health-related quality of life, SE: standard error
Source: Utility survey (see Appendix P)

Table 50: Utilities, EQ-5D - Survey: combined sample child EQ-5D: adolescent self-report: n=38; caregiver proxy-report: n=62

Health state	Child	
	Mean	SE
Current HRQoL	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]

HRQoL: health-related quality of life, SE: standard error
Source: Utility survey (see Appendix P)

Table 51: Interviews, EQ-5D: caregiver-reported child and caregiver EQ-5D (treatment-naïve; n=50)

Health state	Child		Caregiver	
	Mean	SE	Mean	SE
Current HRQoL	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]	[redacted]

HRQoL: health-related quality of life, SE: standard error
Source: Utility survey (see Appendix P)

Table 52: Palforzia survey, EQ-5D: caregiver-reported child and caregiver EQ-5D (Palforzia treated patients; n=7)

Health state	Child		Caregiver	
	Mean	SE	Mean	SE
Pre trial	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 1-4 peanuts	[redacted]	[redacted]	[redacted]	[redacted]

SE: standard error
Source: Utility survey (see Appendix P)

Table 53: Palforzia survey, EQ-5D: combined sample child EQ-5D: adolescent self-report: n=2; caregiver proxy-report: n=5

Health state	Child	
	Mean	SE
Pre trial	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]
Tolerate 1-4 peanuts	[redacted]	[redacted]

SE: standard error
Source: Utility survey (see Appendix P)

To estimate final utility values for the base case, results of surveys and interviews for child and caregivers were pooled (alternative utility value assumptions are explored in model scenarios). Adolescent self-reported values were included in the pooled results instead of their caregiver proxy-reported value where available. For caregivers, a decrease of utility between the state with the highest utility ('Tolerate 6-8 peanuts/ Tolerate 1-4 peanuts') and other states was calculated. Results are presented in Table 54, below.

Table 54: Utilities – pooled (base case; treatment naïve survey + interviews + Palforzia survey, n=157)

	Child		Caregiver		Disutility for caregiver
	Mean	SE	Mean	SE	
Current HRQoL (naïve patients)/pre-trial (treated patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Value for 'Tolerate 1-4 peanuts' from Caregiver-reported (Palforzia survey) was used
HRQoL: health-related quality of life, SE: standard error
Source: Utility survey (see Appendix P)

In the model, the following assumptions are made:

- Values obtained for 'Current HRQoL' in the treatment-naïve samples are used for 'Tolerated dose of peanut protein <300 mg'
- Values obtained for 'Up-dosing' and 'Maintenance" are used for 'Up-dosing' and 'Maintenance' health states, respectively.
- Values obtained for 'Tolerate 6-8 peanuts' are used for 'Tolerated dose of peanut protein 2000 mg'
- For health states with levels of severity between tolerated dose of peanut protein 300 mg and tolerated dose of peanut protein 2000 mg, it was assumed that a linear improvement in quality of life was seen. The difference between utility in the 'Maintenance' and 'Tolerated dose of peanut protein 2000 mg' is distributed evenly between health states with maximum tolerated peanut protein dose of 300 mg, 600 mg and 1000 mg.

- Patients in ‘Spontaneous tolerance’ and ‘Regular inclusion of peanut in diet’ health states will have the same utility as patients in ‘Tolerated dose of peanut protein 2000 mg’ (based on expert opinion from the SHELF elicitation exercise).
- Patients who discontinue Palforzia or regular inclusion of peanut in diet and revert to ‘avoidance only’ will have the same utility as patients in ‘Tolerated dose of peanut protein <300 mg’ (based on expert opinion from the SHELF elicitation exercise).

Values used in the scenario analysis are presented in the table below.

Table 55: Utilities – pooled (scenario analysis; without Palforzia survey, n=150)

	Child		Caregiver		Disutility for caregiver
	Mean	SE	Mean	SE	
Current HRQoL (naïve patients)/pre-trial (treated patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Value for ‘Tolerate 1-4 peanuts’ from Caregiver-reported (Palforzia survey) was used
HRQoL: health-related quality of life, SE: standard error

Quality of life was incorporated for both children with peanut allergy and their caregivers. It was assumed that the quality-of-life implications to caregivers only occur until the patient turns 18. It was estimated that patients have [redacted] carers based on the results from the utility survey mentioned above (calculated as a weighted average of results from survey and interviews, see Table 56 below).

Table 56: Number of caregivers per child with peanut allergy

Number of individuals providing informal care per child	Treatment naïve survey (N=100)	Interviews (N=50)	Palforzia survey (n=7)	Total (n=157)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more*	[redacted]	[redacted]	[redacted]	[redacted]
Average	[redacted]			

*A conservative assumption of 3 carers was included in calculation of the average
Source: Utility survey (see Appendix P)

The total utility applied in each health state is described in Table 57.

Table 57: Utilities included in the CEM (base case)

	Utility	Carer disutility	Total utility (Utility + disutility for [redacted] carers)
Treatment up-dosing	[redacted]	[redacted]	[redacted]
Treatment maintenance	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein <300 mg	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 300 mg	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 600 mg	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 1000 mg	[redacted]	[redacted]	[redacted]
Tolerated dose of peanut protein 2000 mg	[redacted]	[redacted]	[redacted]
Spontaneous tolerance	[redacted]	[redacted]	[redacted]
Regular inclusion of peanut in diet	[redacted]	[redacted]	[redacted]

CEM: cost-effectiveness model

Given the lifetime time horizon in the model, it is necessary to account for the change in quality of life of patients over time. As patients age, it cannot be expected that they have the same utility potential as they did at the model baseline due to deteriorating health. The total patient utility is adjusted for patient age, according to the model of the relationship of utility and age developed by Ara and Brazier (2010).[131] The adjustment is made multiplicatively to ensure potential utility attained is reduced over time.

3.4.5 Disutility from reactions to accidental exposure to peanuts

There is a paucity of evidence available for the utility associated with peanut allergic reactions. Carroll and Downs reported parent preferences according to the parent utility of their child experiencing a moderate or severe allergic reaction, 0.93 and 0.91, respectively.[130] According to a baseline utility of 1.00 for parents, this incurs a disutility of 0.07 and 0.09 for moderate and severe allergic reactions, respectively. Given the lack of evidence specific to patients, this source was used. Disutility of moderate allergic reaction was used for 'Reactions to accidental exposure to peanut requiring treatment not with adrenaline' disutility of severe allergic reactions was used for 'Reactions to accidental exposure to peanut requiring adrenaline'.

The duration of the disutility was assumed to be proportionate to the event; it is assumed the disutility lasts for 1 day in all 'Reactions to accidental exposure to peanut requiring treatment not with adrenaline' and 2 days in 'Reactions to accidental exposure to peanut requiring adrenaline', respectively (based on expert opinion). The

disutility applied to reactions to accidental exposures to peanut protein is summarised in Table 58.

Table 58: Disutilities due to accidental exposure to peanut

Reaction	Disutility	Disutility duration (days)	Total disutility
Reactions to accidental exposure to peanut requiring treatment not with adrenaline	0.07	1	0.0002
Reactions to accidental exposure to peanut requiring treatment with adrenaline	0.09	2	0.0005

Source: Carroll and Downs (2009)[130]

3.4.6 Treatment-related adverse events

Disutilities associated with mild and moderate treatment-related anaphylactic reactions and moderate TRAEs are included in the model (Table 59).

It was assumed that disutility due to mild and moderate anaphylactic reactions would be similar to the disutility for severe allergic reaction (0.09, Carroll and Downs (2009)[130]).

It was assumed that disutility due to non-anaphylactic moderate TEAEs would be similar to the disutility reported by Carroll and Downs (2009)[130] for moderate allergic reaction (0.07, Carroll and Downs (2009)[130]).

Disutility values and duration were validated by the clinical expert.

Table 59: Disutilities due to treatment-related adverse events

Adverse event/reaction	Disutility	Disutility duration (days)	Total disutility
Anaphylactic reactions			
Mild anaphylactic reaction	0.09	2	0.0005
Moderate anaphylactic reaction	0.09	2	0.0005
Other adverse events			
Moderate gastrointestinal disorders*	0.07	1	0.0002
Moderate respiratory, thoracic and mediastinal disorders**	0.07	1	0.0002
Moderate skin and subcutaneous tissue disorders#	0.07	1	0.0002

TRAE: treatment-related adverse event
* The most frequent events were: Abdominal pain, Oral pruritus, Abdominal pain upper, Nausea, Vomiting, Paraesthesia oral, Abdominal discomfort, Tongue pruritus, Lip pruritus, Lip swelling.
** The most frequent events were: Throat irritation, Cough, Throat tightness, Sneezing, Rhinorrhoea, Wheezing, Nasal congestion, Dyspnoea, Oropharyngeal pain, Pharyngeal paraesthesia.

#The most frequent events were: Pruritus, Urticaria, Rash, Swelling face, Erythema, Eczema, Rash erythematous, Angioedema.
Source: Carroll and Downs (2009)[130]

3.4.7 Summary

Table 60: Summary of utility values for cost-effectiveness analysis (patient utility and caregiver disutility combined)

State	Utility value (with carer disutility)	Reference in submission (section and page number)	Justification
Treatment up-dosing	[redacted]	Section B.3.4.4	Utility survey
Treatment maintenance	[redacted]	Section B.3.4.4	Utility survey
Tolerated dose of peanut protein <300 mg	[redacted]	Section B.3.4.4	Utility survey
Tolerated dose of peanut protein 300 mg	[redacted]	Section B.3.4.4	Utility survey
Tolerated dose of peanut protein 600 mg	[redacted]	Section B.3.4.4	Utility survey
Tolerated dose of peanut protein 1000 mg	[redacted]	Section B.3.4.4	Utility survey
Tolerated dose of peanut protein 2000 mg	[redacted]	Section B.3.4.4	Utility survey
Spontaneous tolerance	[redacted]	Section B.3.4.4	Assumption based on experts opinion
Regular inclusion of peanut in diet	[redacted]	Section B.3.4.4	Assumption based on experts opinion
Reactions to accidental exposure to peanut requiring treatment not with adrenaline	-0.0002	Section B.3.4.5	Based on literature and expert opinion
Reactions to accidental exposure to peanut requiring treatment with adrenaline	-0.0005	Section B.3.4.5	Based on literature and expert opinion
Mild and moderate treatment related anaphylactic reactions	-0.0005	Section B.3.4.6	Based on literature and expert opinion
All other non-anaphylactic TRAEs	-0.0002	Section B.3.4.6	Based on literature and expert opinion

TRAE: treatment-related adverse event

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix I describes the results of cost and healthcare resource SLR.

The model is built structurally to include direct healthcare costs, in line with the NHS and PSS perspective, and indirect costs for the societal perspective, for adaption to future markets.

In the model, following cost categories are included:

- Drug costs,
- Administration costs,
- Disease management costs (e.g. routine appointments),
- Treatment-related adverse event costs,
- Accidental exposure to peanut treatment costs,

3.5.1 Palforzia – drug and administration costs

A [redacted] per day was applied for each dose of Palforzia (range 0.5–300 mg), consequently any dose reduction does not impact on the cost. The actual number of doses taken by patients does not always equal the prescribed dose, some patients may miss doses and administer less treatment than prescribed. This decreases the total cost of treatment. In the PALISADE study, the proportion of prescribed doses taken by patients was [redacted], therefore compliance has been included in the model at this rate.[39]

Table 61 shows the treatment acquisition costs for Palforzia, avoidance and maintaining peanut in diet.

Table 61: Drug costs per day

Intervention	Daily drug cost	Compliance
Palforzia	[redacted]	[redacted]
Avoidance	£0	Not relevant
Peanuts in diet	£0	Not relevant

Palforzia should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases. Initial dose escalation and the first dose of each new up-dosing level are therefore administered in a health care setting prepared to manage potential severe allergic reactions. Within the model the following assumptions were made:

- Up-dosing, initial dose escalation (1st cycle in the model, duration: 1 day): day case appointment (first day)),
- Up-dosing, subsequent cycles (duration of cycles: 14 days): For the first up-dosing to a new Palforzia dose a visit is required. Further doses are taken without observation and do not require follow–up visits.
- Maintenance: During maintenance and extended time horizon there is no requirement for dose appointments and thus the administration costs are assumed to be zero for patients in these phases.

For the first initial escalation visit resource utilisation is presented in Table 62 below. Hourly wages for different specialists' time were extracted from the Personal Social Services Research Unit.[132] As a result, it was estimated that cost of first initiation visit for administration of Palforzia is £485.

Table 62: First initial escalation visit for Palforzia administration

Type of specialist	Duration (hours)	Unit cost per hour (GBP)	Comment/Source
Allergist education	0.5	119	PSSRU 2020 - Hospital-based doctors: Consultant
Allergist administration of Palforzia	1.0	50	PSSRU 2020 - Hospital-based doctors: Registrar
Nurse administration	3.5	50	PSSRU 2020 - Hospital-based nurses: 50% - band 7-8 nurse, 50% - band 4-5 nurse
Nurse monitoring	4.0	50	PSSRU 2020 - Hospital-based nurses: 50% - band 7-8 nurse, 50% - band 4-5 nurse
Total cost		485	

PSSRU: Personal Social Services Research Unit

For all follow-up visits a cost of £192 was assumed (cost of Service 313 'Clinical Immunology and Allergy Service', *NHS reference costs 2018/2019*).[133] This is a conservative approach compared with summing up the individual costs of resources use. Specifically, a typical up-dosing visit would be expected to involve 2 hours of nurse supervision and 10 minutes education from a registrar level allergist, which would equate to a cost of £108 per visit based on the above unit costs. The conservative approach was used in order to cover any variability in resource use e.g. additional administration and dealing with queries from caregivers.

Costs of the initial escalation and follow-up visit were discussed and validated by a clinical expert.

Total costs of Palforzia administration are summarised in Table 63.

Table 63: Total Palforzia drug cost per cycle

Cycle	Acquisition costs per cycle (£)	Administration cost per cycle (£)	Total cost per cycle (£)
Up-dosing, First cycle - Initial escalation dose (duration: 1 day)	[redacted]	485	[redacted]
Up-dosing, next cycles (duration: 14 days)	[redacted]	192	[redacted]
Maintenance (duration: 28 days)	[redacted]	0	[redacted]
Extrapolation (duration: 1 year)	[redacted]	0	[redacted]

3.5.2 Avoidance only, regular inclusion of peanut in diet – drug and administration costs

No drug costs and administration costs for avoidance only and regular inclusion of peanut in diet was assumed.

3.5.3 Food challenge following successful treatment with Palforzia

It was assumed that after two years of successful treatment, patients treated with Palforzia might optionally have an open food challenge (i.e. not a DBPCFC which is mainly used in trials) to assess a maximum level of peanut protein tolerance. Knowledge of how much peanut protein can be tolerated can help to reduce uncertainty and fear about accidental exposures to peanut, and therefore improve patient and caregiver HRQoL as demonstrated in the utility survey study.

In the model, a cost of £276.34 was assumed for a food challenge. This value was extracted from the NICE guideline ImmunoCAP ISAC 112 for multiplex allergen testing (£256 which represent the cost of an oral-food-challenge test in the NHS, inflated).[134]

In the base case it was assumed that all patients who completed two years of Palforzia treatment would have a food challenge. This is a conservative assumption, as in real life, it is likely that many patients would not want to undergo a food challenge. No food challenge was assumed for avoidance only.

3.5.4 Routine monitoring and other costs

The cost and healthcare resource SLR identified a wide range of costs and resource use, including the costs associated with accidental peanut exposure and ongoing management of peanut allergy.[58,135] The cost and resource use identified in the SLR were predominantly from the US perspective, with one paper reporting the costs or resource use in the UK, previously discussed in section 1.3.3.[9]

In the model the following resources were included in the estimation of routine monitoring and other costs in different health states:

- Allergist appointments,
- Dietitian appointments,
- Pulmonologist appointments,
- Routine paediatrician/GP appointments,
- Prescribed adrenaline,
- Antihistamine (high-dose antihistamine [HDA]) use.

The annual number of visits per each health state was provided by a clinical expert. It was assumed that:

- All patients will have one allergist visit per year,
- All patients will have one dietitian consultation per year,
- There will be no GP/paediatrician visits for follow-up monitoring,
- Around 10% of patients will require an additional specialist visit (patients with asthma – pulmonologist visit).
- Aside from unscheduled resource use for TRAEs and accidental exposures to peanuts requiring treatment, resource utilisation will be same for both included interventions (Palforzia and avoidance alone) and for all health states, except for ‘Spontaneous tolerance’ health state. Based on expert opinion, the healthcare professional monitoring schedule does not depend on the level of peanut protein tolerance. Both patients on Palforzia and those on strict avoidance should be monitored with the same visit frequency.

- There will be no peanut allergy related visits and resource utilisation in the 'Spontaneous tolerance' health state. Based on the expert opinion, patients who become spontaneously tolerant will not require monitoring of peanut allergy.

Additionally, NHS resources indicate that patients in the UK may be prescribed two adrenaline autoinjectors and take antihistamines routinely.[136] Based on the UK expert opinion, it is assumed that patients would be prescribed four adrenaline autoinjectors per year (two for use at home and two for use at school).

The costs associated with disease management were sourced from national databases: the cost of an adrenaline autoinjector and high-dose antihistamine (HDA) was sourced from the British National Formulary (BNF) whilst the cost of appointments with medical practitioners was sourced from the NHS reference costs 2018/2019.[133,137]

The costs and resource use associated with disease management used in the model are summarised in Table 64.

Table 64: Disease management costs and resource use per year

Resource	Unit cost (£)	Health state	Resource use per year	Resource use source	Cost source
Adrenaline	34.30	Treatment up-dosing	4	Expert opinion + MHRA Adrenaline auto-injectors: advice on use May 2014: (The brand names of adrenaline auto-injectors currently available in the UK are Emerade, EpiPen, and Jext)	BNF - Adrenaline (Drug tariff price for Emerade, EpiPen, and Jext; all products 300 micrograms/0.3ml)
		Treatment maintenance	4		
		Tolerated dose of peanut protein <300 mg	4		
		Tolerated dose of peanut protein 300 mg	4		
		Tolerated dose of peanut protein 600 mg	4		
		Tolerated dose of peanut protein 1000 mg	4		
		Tolerated dose of peanut protein 2000 mg	4		
		Eating peanuts	4		
		Spontaneous tolerance	0		
Routine paediatrician appointment	229	Treatment escalation	0	Expert opinion	NHS reference costs 2018/2019 – Outpatient Attendances Data - service code 255: Paediatric Clinical Immunology and Allergy Service
		Treatment maintenance	0		
		Tolerated dose of peanut protein <300 mg	0		
		Tolerated dose of peanut protein 300 mg	0		
		Tolerated dose of peanut protein 600 mg	0		
		Tolerated dose of peanut protein 1000 mg	0		
		Tolerated dose of peanut protein 2000 mg	0		
		Eating peanuts	0		

		Spontaneous tolerance	0		
Allergist appointment	192	Treatment escalation	1	Expert opinion	NHS reference costs 2018/2019 – Outpatient Attendances Data - service code 313: Clinical Immunology and Allergy Service
		Treatment maintenance	1		
		Tolerated dose of peanut protein <300 mg	1		
		Tolerated dose of peanut protein 300 mg	1		
		Tolerated dose of peanut protein 600 mg	1		
		Tolerated dose of peanut protein 1000 mg	1		
		Tolerated dose of peanut protein 2000 mg	1		
		Eating peanuts	1		
		Spontaneous tolerance	0		
Nutritionist appointment	90	All health states except ‘Spontaneous tolerance’	1	Expert opinion	NHS reference costs 2018/2019 – Other Currencies Data - service code A03: Dietitian
		‘Spontaneous tolerance’	0		
Pulmonologist appointment	216	All health states except ‘Spontaneous tolerance’	0.1	Expert opinion	NHS reference costs 2018/2019 – Outpatient Attendances Data - service code 258: Paediatric Respiratory Medicine
		‘Spontaneous tolerance’	0		
HDA	0.44	All health states*	0	Expert opinion	BNF - drug tariff for Cetirizine hydrochloride 10 mg - capsules (7 capsules - £3.09); the most costly drug was used (cost per dose) from following possible antihistamies: cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine

Total cost per year per health state	Treatment escalation	£441	---	---
	Treatment maintenance	£441		
	Tolerated dose of peanut protein <300 mg	£441		
	Tolerated dose of peanut protein 300 mg	£441		
	Tolerated dose of peanut protein 600 mg	£441		
	Tolerated dose of peanut protein 1000 mg	£441		
	Tolerated dose of peanut protein 2000 mg	£441		
	Regular inclusion of peanut in diet	£441		
	Spontaneous tolerance	£0		

*There is functionality to include these costs, however, under the base case assumptions no patients receive these resources.
BNF: British National Formulary; HDA: high-dose antihistamines; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health service.

3.5.5 Reactions to accidental exposure to peanut costs

Due to differences in resource utilisation and disutilities, reactions to accidental exposures to peanut were categorised into two groups:

- Reactions to accidental exposure to peanuts that require treatment with adrenaline,
- Reactions to accidental exposure to peanuts that require treatment but not requiring adrenaline.

Based on the existing guidelines,[42,138] it was assumed that all accidental exposures to peanut that required adrenaline use will be followed by ambulance use and A&E visit.

Use of other resources (inpatient stay, HDA, and adrenaline) associated with treatment of reactions to accidental peanut exposures was provided by a clinical expert.

Cost of ambulance service was extracted from National Audit Office NHS Ambulance Services report. In 2015-16, the average cost per call across the ambulance service was around £190, and the cost per attendance was around £270.[139] In the model total cost of £496.54 was assumed for ambulance service (call + attendance, uplifted using the Consumer Price Index (CPI)).[140]

The costs associated with A&E visits and inpatient stays are sourced from NHS reference costs 2018-2019:[133]

- A&E visit: Outpatient Attendances Data - Service code 180: Accident & Emergency - £168.
- Inpatient stay: HRG WH05Z - Allergy or Adverse Allergic Reaction, non-elective short stay - £319.

The cost of HDA and adrenaline is sourced from the British National Formulary (BNF).[137] A full breakdown of the costs and resource use associated with adverse reactions to accidental exposures to peanut protein is given in Table 65.

Table 65: Summary of reaction to accidental exposure costs

Component of cost	Unit cost (£)	Unit cost source	Resource use for adverse reactions to accidental exposure to peanut	
			With adrenaline	Without adrenaline
Ambulance	496.54	National Audit Office NHS Ambulance Services report,[139] Inflated using CPI[140]	100%	10%
A&E visit	168.00	NHS reference costs 2017-2018[133]	100%	5%
Inpatient stay	319.00	NHS reference costs 2017-2018[133]	10%	0%
HDA	0.44	BNF - BNF - Cetirizine hydrochloride 10 mg - capsules (7 capsules - £3.09)	100%	100%
Adrenaline (1 single replacement)	34.30	BNF- Adrenaline	100%	0%
Total cost per event (£)			731.19	58.50

A&E: accident and emergency; BNF: British National Formulary; CPI: Consumer Price Index; ERG: Evidence Review Group; HDA: high-dose antihistamines; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

3.5.6 TRAEs unit costs and resource use

Treatment related anaphylactic reactions

It was assumed that all mild and moderate treatment-related anaphylactic reactions will require adrenaline injections. Use of other resources (ambulance, inpatient stay, HDA, and adrenaline) associated with treatment of anaphylactic reactions was provided by a clinical expert.

A full breakdown of the costs and resource use associated with a treatment of treatment-related anaphylactic reactions is given in Table 66.

Table 66: Summary of treatment-related anaphylactic reaction costs

Component of cost	Unit cost (£)	Unit cost source	Resource use for treatment of anaphylactic reactions	
			Mild	Moderate
Ambulance	496.54	National Audit Office NHS Ambulance Services report,[139] Inflated using CPI[140]	10%	50%
A&E visit	168.00	NHS reference costs 2017-2018[133]	20%	70%

Inpatient stay	319.00	NHS reference costs 2017-2018[133]	5%	50%
HDA	0.44	BNF Cetirizine hydrochloride 10 mg - capsules (7 capsules - £3.09)	0%	5%
Adrenaline (1 single replacement)	34.30	BNF- Adrenaline	100%	100%
Total cost per event (£)			133.50	559.69

A&E: accident and emergency; BNF: British National Formulary; CPI: Consumer Price Index; HDA: high-dose antihistamines; NHS: National Health Service;

Treatment related non-anaphylactic adverse events

The most frequent treatment-related adverse events reported in the PALISADE trial were:[39]

- Gastrointestinal disorders: abdominal pain, oral pruritus, abdominal pain upper, nausea, vomiting, paraesthesia oral, abdominal discomfort, tongue pruritus, lip pruritus, lip swelling.
- Respiratory, thoracic and mediastinal disorders: throat irritation, cough, throat tightness, sneezing, rhinorrhoea, wheezing, nasal congestion, dyspnoea, oropharyngeal pain, pharyngeal paraesthesia.
- Moderate skin and subcutaneous tissue disorders: pruritus, urticaria, rash, swelling face, erythema, eczema, rash erythematous, angioedema.

A clinical expert confirmed that, the majority of non-anaphylactic treatment related moderate adverse events can be managed at home with antihistamines. Additionally, it is expected that a patient/carer will seek phone call advice with an allergist. Based on the expert opinion it was assumed that a 10 minute phone call would be sufficient to report and receive advice on adverse events.

The unit cost for HDA of £0.44 was obtained from the BNF (drug tariff for Cetirizine hydrochloride 10 mg - capsules (7 capsules - £3.09); the most costly drug was used (cost per dose) from following possible antihistamines: cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine).[137] Costs of a phone call were estimated based on allergist costs reported in the PSSRU 2020 (cost per 1 hour of allergist, average of registrar and consultant costs - £50 and £119 respectively, 10 minutes - £14.08).[132]

Summary of costs assumed for treatment of TRAEs is presented in the Table 67.

Table 67: Summary of non-anaphylactic TRAEs costs

Adverse event	Unit cost (£)	Source	Comment
Moderate gastrointestinal disorders	14.52	Expert opinion, PSSRU 2020 (cost of phone call), BNF (HDA)	HDA + 10 minutes of phone call with allergist (average of a registrar and consultant)
Moderate respiratory, thoracic and mediastinal disorders	14.52	Expert opinion, PSSRU 2020 (cost of phone call), BNF (HDA)	HDA + 10 minutes of phone call with allergist (average of a registrar and consultant)
Moderate skin and subcutaneous tissue disorders	14.52	Expert opinion, PSSRU 2020 (cost of phone call), BNF (HDA)	HDA + 10 minutes of phone call with allergist (average of a registrar and consultant)

BNF: British National Formulary; CC: complications; HDA: high-dose antihistamine; NHS: National Health Service; PSSRU: Personal Social Services Research unit

3.5.7 Miscellaneous unit costs and resource use

No other costs than those mentioned in sections above were included in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

3.6.1 Summary of base-case analysis inputs

Table 68: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline characteristic			
Mean age (years)	10	No distribution	Table 30
Model structure			
Time horizon	Lifelong (90 years)	No distribution	Section B.3.2.6
Cycle length	Initial dose escalation: 1 cycle - 1 day Up-dosing: 20 cycles – 14 days each Maintenance: 8 cycles – 28 days each Extension: 1 cycle – 224.5 days Extrapolation – annual cycles	No distribution	Section B.3.2.10

Discounting rates	3.5% clinical outcomes 3.5% costs	No distribution	Section B.3.2.7
Clinical efficacy			
Palforzia – proportion of patients transitioning to 'Tolerated dose of peanut protein <300 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia – proportion of patients transitioning to 'Tolerated dose of peanut protein 300 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia – proportion of patients transitioning to 'Tolerated dose of peanut protein 600 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia – proportion of patients transitioning to 'Tolerated dose of peanut protein 1000 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia – proportion of patients transitioning to 'Tolerated dose of peanut protein 2000 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Avoidance only – proportion of patients transitioning to 'Tolerated dose of peanut protein <300 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Avoidance only – proportion of patients transitioning to 'Tolerated dose of peanut protein 300 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Avoidance only – proportion of patients transitioning to 'Tolerated dose of peanut protein 600 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Avoidance only – proportion of patients transitioning to 'Tolerated dose of	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2

peanut protein 1000 mg', Week 72			
Avoidance only – proportion of patients transitioning to 'Tolerated dose of peanut protein 2000 mg', Week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia - proportion of patients transitioning to 'Tolerated dose of peanut protein <300mg', after week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia - proportion of patients transitioning to 'Tolerated dose of peanut protein 300mg', after week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia - proportion of patients transitioning to 'Tolerated dose of peanut protein 600mg', after week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia - proportion of patients transitioning to 'Tolerated dose of peanut protein 1000mg', after week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Palforzia - proportion of patients transitioning to 'Tolerated dose of peanut protein 2000mg', after week 72	[redacted]	Dirichlet distribution, calculated from PLD	Section B.3.3.2
Lifetime probability of transitioning to 'Spontaneous tolerance'	5%	Beta distribution calculated by using mean=5%, SE=10% of mean	Section B.3.3.2
Frequency of reactions to accidental exposure to peanuts	Stratified by interventions and by health state	Beta distribution calculated separately for each intervention and health state, using SE=10% of reported value	Section B.3.3.3
Adverse events			
TRAEs and treatment-related anaphylactic reaction rates	Stratified by interventions and by health state	Beta distribution calculated separately for each intervention and health state, using	Section B.3.3.4

		SE=10% of reported value	
Duration of Palforzia treatment			
Proportion of patients continuing Palforzia long-term	[redacted]	No distribution, calculated as 100% minus 'Proportion of patients transition to regular inclusion of peanut in diet'	Section B.3.3.6
Proportion of patients transition to regular inclusion of peanut in diet (P1)	[redacted]	Distribution Beta([redacted] – SHELF elicitation exercise	Section B.3.3.6
Proportion of patients transition from regular inclusion of peanut in diet into avoidance alone (P2)	[redacted]	Distribution Beta[redacted] – distribution not provided in the SHELF elicitation exercise, Beta distribution calculated by using mean=29%, SE=50% of mean to include higher uncertainty around this parameter	Section B.3.3.6
Utilities			
Treatment escalation	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Treatment maintenance	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Tolerated dose of peanut protein <300 mg	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Tolerated dose of peanut protein 300 mg	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Tolerated dose of peanut protein 600 mg	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Tolerated dose of peanut protein 1000 mg	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Tolerated dose of peanut protein 2000 mg	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Spontaneous tolerance	[redacted]	Beta distribution calculated by using	Section B.3.4.4

		mean and SE from the Utility survey	
Regular inclusion of peanut in diet	[redacted]	Beta distribution calculated by using mean and SE from the Utility survey	Section B.3.4.4
Number of carers included in disutility calculations	[redacted]	Gamma distribution calculated by using mean=[redacted] and SE=10% of mean	Section B.3.4.4
Disutility for Reactions to accidental exposure to peanut requiring treatment not with adrenaline'	0.0002	Beta distribution for disutility, Gamma distribution for duration of disutility, calculated by using SE=10% of mean	Section B.3.4.4
Disutility for Reactions to accidental exposure to peanut requiring treatment with adrenaline'	0.0005	Beta distribution for disutility, Gamma distribution for duration of disutility, calculated by using SE=10% of mean	Section B.3.4.4
Disutility for treatment-related mild anaphylactic reaction and for moderate anaphylactic reaction	0.0005	Beta distribution for disutility, Gamma distribution for duration of disutility, calculated by using SE=10% of mean	Section B.3.4.4
Disutilities for other non-anaphylactic TRAEs	0.0002	Beta distribution for disutility, Gamma distribution for duration of disutility, calculated by using SE=10% of mean	Section B.3.4.4
Costs			
Daily cost of Palforzia	[redacted]	Gamma distribution calculated separately for each treatment phase by using SE=10% of mean	Section B.3.5.1
Daily cost of 'Avoidance only'	£0	No distribution	Section B.3.5.2
Daily cost of 'regular inclusion of peanut in diet'	£0	No distribution	Section B.3.5.2
Administration of Palforzia - First cycle - Initial escalation dose	£485	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.1
Administration of Palforzia – Up-dosing, next cycles	£192	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.1
Administration of Palforzia – Other health states	£0	No distribution	Section B.3.5.1

Administration costs for avoidance only and regular inclusion of peanut in diet	£0	No distribution	Section B.3.5.2
Food challenge	£276.34	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.3
Treatment monitoring	£0 – Spontaneous tolerance £441 – other health states	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.4
Non-anaphylactic moderate TRAEs	£14.52	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.6
Mild treatment-related anaphylactic reaction	£133.50	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.6
Moderate treatment-related anaphylactic reaction	£559.69	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.6
Reactions to accidental exposure to peanuts with adrenaline	£731.19	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.5
Reactions to accidental exposure to peanuts without adrenaline	£58.50	Gamma distribution calculated by using SE=10% of mean	Section B.3.5.5

TRAE: treatment related adverse event; CI: confidence interval, SE: standard error.

3.6.2 Assumptions

Table 69: Summary of assumptions applied in the economic model

Assumption	Justification
Time horizon and cycle length	
The model adopts a lifetime horizon with variable cycles based on the initial escalation, up-dosing and maintenance schedules of Palforzia.	Time horizon in line with previously published models in peanut allergy. The cycle length is in line with when data is to be captured for Palforzia, and the likely administration schedule in clinical practice.
Model structure	
The Markov assumption is applied, i.e. the probability of transitioning to a future state is based on the current state and not previous states.	No evidence to suggest previous severity of reaction predicts future severity of reaction, and this assumption has been verified by a clinical expert.
The important costs and consequences associated with peanut allergy can be captured by sensitivity to peanut protein.	Published literature and expert opinion.

Clinical effectiveness	
Data from clinical trials were used to calculate transition probabilities in the first 2 years of treatment.	CSRs, patient level data
Extrapolation of outcomes past the clinical trial data are based on data from the Palforzia studies, expert opinion and literature.	Standard methodology for extrapolating trial data, validated by expert opinion.
No further clinical benefit in terms of increased level of desensitisation to peanut was applied for patients who will continue Palforzia beyond 2 years.	Conservative assumption, no evidence to support further benefit.
Duration of Palforzia treatment	
After [redacted] years of Palforzia treatment Palforzia patients may stay on treatment, switch to regular inclusion of peanut in diet or return to avoidance only.	SHELF expert elicitation exercise
Cost and resource use	
Relevant cost categories include drug costs, administration costs, disease management costs, reactions to accidental exposure to peanut, moderate to severe adverse event costs are included.	Published literature and expert opinion.
Quality of life inputs	
Quality of life parameters include patient utility and caregiver utility.	Utility survey
Disutilities due to adverse events and reactions to accidental exposure to peanut are applied.	Published literature and expert opinion.

CSR: clinical study report, SHELF: Sheffield Elicitation Framework

B.3.7 Base-case results

3.7.1 Base-case incremental cost-effectiveness analysis results

Aggregated base case results for the cost-effectiveness of Palforzia compared to avoidance are presented in

Table 70. Over the lifetime time horizon, treatment with Palforzia was associated with 20.000 QALYs at a cost of £33,172, and avoidance alone strategy accrued 19.084 QALYs at a cost of £11,973. This corresponds to 0.916 incremental QALYs at an incremental cost of £21,199 for Palforzia compared with avoidance. The ICER for Palforzia compared with avoidance only is £23,142 per QALY gained.

Table 70: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,172	26.8	20.000	21,199	0.000	0.916	23,142
Avoidance only	11,973	26.8	19.084				

ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-year.

Disaggregated results are presented in Appendix J.

B.3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) assigned distributions to the model parameters and ran 10,000 simulations to further explore parameter uncertainty.

The cohort size, time horizon, discount rates and treatment cost for Palforzia were kept fixed. The following distributions were used for the relevant parameters:

- Dirichlet distributions were used for transition probabilities between health states (driven by PLD),
- Beta distributions were used for the clinical probabilities (TEAE rates, reactions to accidental exposure to peanuts) and patient health state utilities (standard approach),
- Beta distributions were used for duration of treatment parameters (P1, P2, driven by SHELF elicitation exercise results),
- Gamma distributions were used for drug costs, adverse events costs, compliance, treatment escalation, maintenance and tolerance costs, and disease management and complication costs (standard approach).

Details of selected distributions are presented in Table 68.

Mean incremental results are recorded and illustrated through an incremental cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) is plotted.

Table 71 shows the mean results of the PSA. Results are similar to that of the base case. The incremental cost-effectiveness plane (Figure 27) shows that 99.96% of the

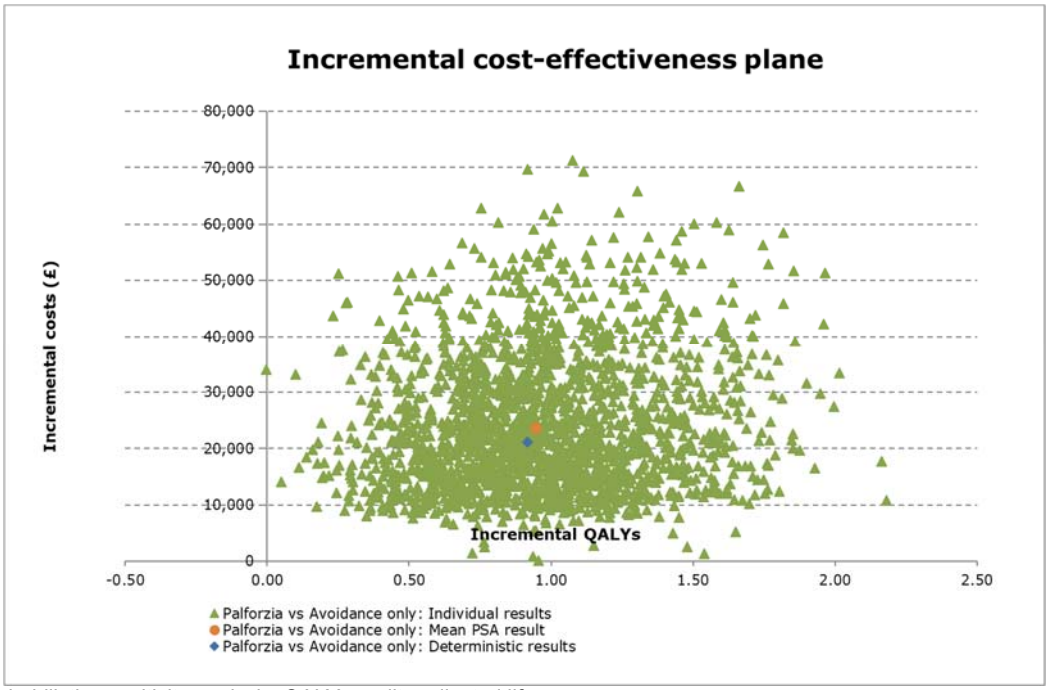
iterations fell in the north east quadrant where Palforzia is more costly and more effective. The CEAC, as presented in Figure 28, illustrates the probability of Palforzia being cost-effective compared to avoidance, at various willingness to pay thresholds. At thresholds of £20,000/QALY and £30,000/QALY, the probability of Palforzia being cost-effective compared to avoidance is 38.3% and 64.4% respectively.

Table 71: PSA results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	35,594	20.014	23,681	0.947	25,011
Avoidance only	11,913	19.067			

ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

Figure 27: Incremental cost-effectiveness plane



PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year

Figure 28: Cost-effectiveness acceptability curve

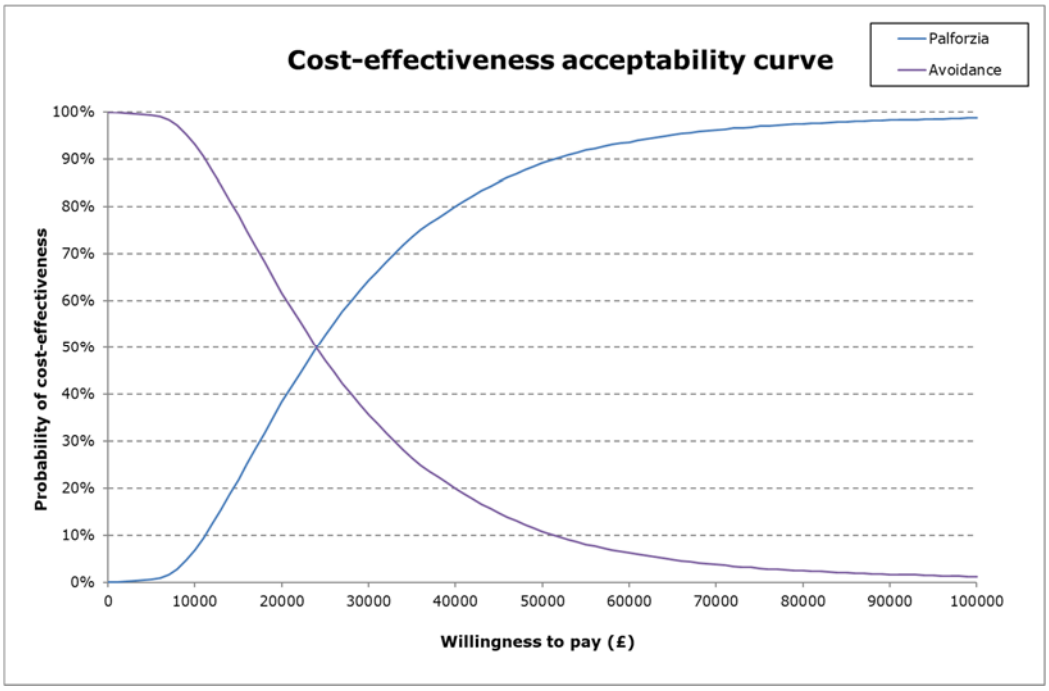
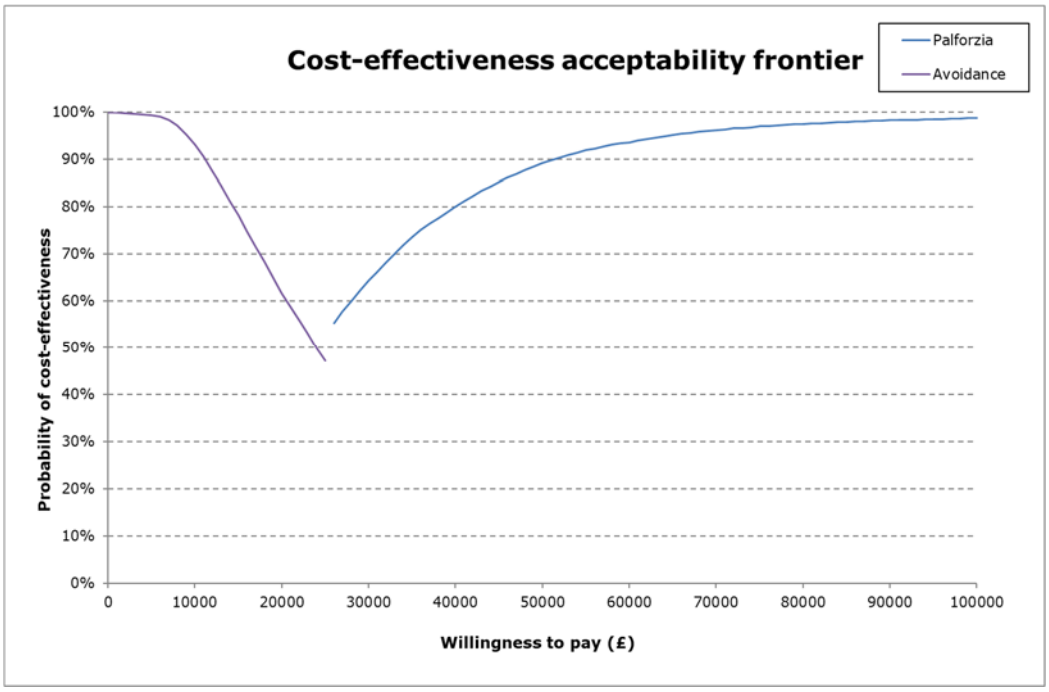


Figure 29: Cost-effectiveness acceptability frontier



3.8.2 Deterministic sensitivity analysis

The one-way sensitivity analysis (OWSA) varied each parameter individually between the upper and lower bounds of confidence intervals within pre-specified probabilistic

distributions assigned to each parameter (Table 72). Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be ±10% of the mean. The results of the model are then evaluated using the upper and lower bounds for each parameter fixing all other values and the overall ICER value is recorded. This provides a measure of which variables have largest impact in the overall cost-effectiveness analysis and provides justification of model robustness under parameter variation.

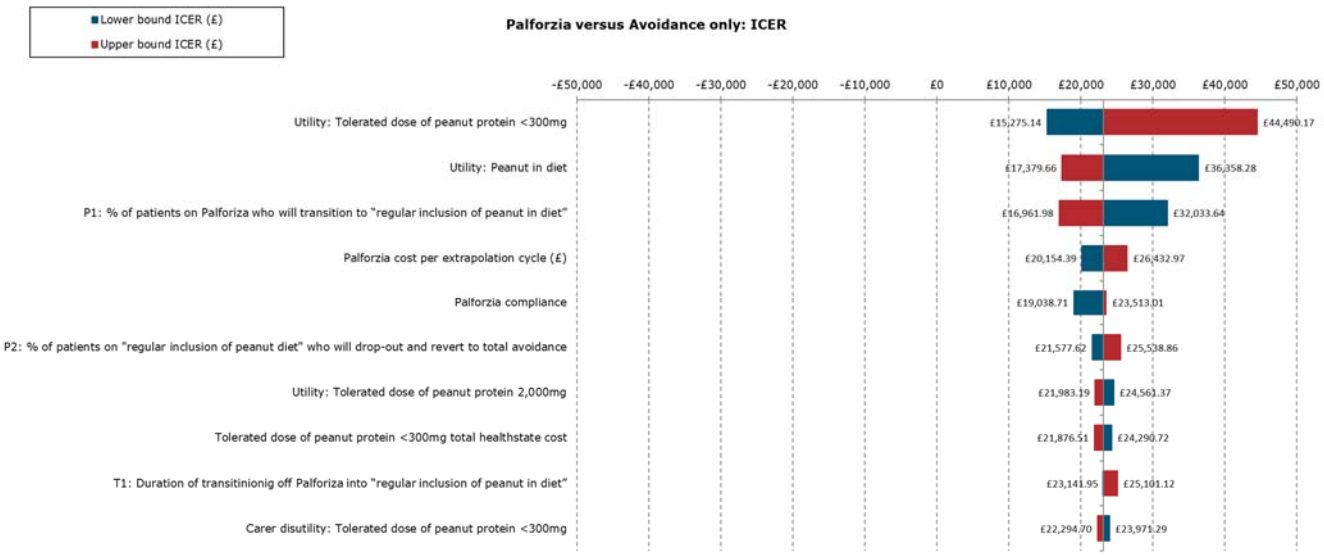
Table 72: Ten main parameters included in the OWSA with the largest impact on results

Parameter	Base case value	Lower bound parameter	Upper bound parameter	Comment
Utility: Tolerated dose of peanut protein <300mg	[redacted]	[redacted]	[redacted]	Based on SE
Utility: Peanut in diet	[redacted]	[redacted]	[redacted]	Based on SE
P1: % of patients on Palforzia who will transition to “regular inclusion of peanut in diet”	[redacted]	[redacted]	[redacted]	25% and 75% percentile
Palforzia cost per extrapolation cycle (£)	[redacted]	[redacted]	[redacted]	[redacted]
Palforzia compliance	[redacted]	[redacted]	[redacted]	+/-10%, 100% upper limit
P2: % of patients on "regular inclusion of peanut diet" who will drop-out and revert to total avoidance	[redacted]	[redacted]	[redacted]	25% and 75% percentile
Utility: Tolerated dose of peanut protein 2,000mg	[redacted]	[redacted]	[redacted]	Based on SE
Tolerated dose of peanut protein <300mg total health state cost	441.24	359.01	531.82	+/-10%
T1: Duration of transitioning off Palforzia into “regular inclusion of peanut in diet”	[redacted]	[redacted]	[redacted]	Assumption
Carer disutility: Tolerated dose of peanut protein <300mg	[redacted]	[redacted]	[redacted]	+/-10%

A tornado diagram was developed to illustrate the level of uncertainty considering the ICER based on the upper and lower bounds.

Figure 30 displays the tornado diagram for the ICER results of the OWSA for the top 10 most sensitive parameters. Results are most sensitive to the utility value associated with patients <300 mg tolerance health state where the lower bound produces an ICER of £15,275 and the upper bound produces an ICER of £44,490. Across all parameters tested except utility value associated with patients <300 mg tolerance health state and utility value associated with patients in 'Regular inclusion of peanut in diet' and P1 value, the ICER remains below the £30,000 per QALY gained threshold.

Figure 30: OWSA tornado diagram



ICER: incremental cost-effectiveness ratio.

3.8.3 Scenario analysis

List of scenarios included in the scenario analyses were presented in Table 73.

Table 73: Scenario analyses

Scenario	Justification & scenarios description
Time horizon	Given the variability of time horizons used in the literature, assessing the influence of different time horizons will allow a robust assessment of cost-effectiveness. Time horizons included in the scenario analyses: **Scenario 1**: 5 years **Scenario 2**: 20 years
Source of clinical data	Data from the ARTEMIS trial were used in the scenario analysis. Inputs are described in the Appendix O. **Scenario 3**: inputs from the ARTEMIS trial

Long-term outcomes	Different assumptions regarding long-term outcomes in terms of transition to inclusion of peanut in diet, reverting to avoidance only and duration of these transitions were explored, based on the SHELF exercise. Following scenarios were investigated: **Scenario 4**: [redacted] Scenarios 5-7 are as per scenario 4 but proportion of patients transitioning to inclusion of peanut in diet, reverting to avoidance only, and the duration of such transitions are varied as follows: **Scenario 5**: [redacted] **Scenario 6**: [redacted] **Scenario 7**: [redacted]
Utilities	Utilities estimation has the biggest impact on results (see OWSA). Impact of different utilities assumptions were investigated. Following scenarios were included: **Scenario 8**: Utilities pooled from the utility survey with results from Palforzia-treated participants excluded (Table 55) **Scenario 9**: Utilities from the n=50 interviews only (Table 51) **Scenario 10**: The same utility is maintained across all health states in the avoidance arm (as in the <300 mg tolerated dose health state). In real-life, patients following an avoidance only strategy would not experience the disutility of up-dosing, but equally the small percentage of

	avoidance arm patients who tolerated ≥300mg in the PALISADE exit DBPCFC would not have been aware in real-life, hence would not have experienced associated utility gains.
Carers	There is limited evidence to support the number of carers associated with patients with peanut allergy, therefore the base-case assumption is reviewed. **Scenario 11**: 1 carer per patient **Scenario 12**: 2 carers per patient

SHELF: Sheffield Elicitation Framework

The ICER range obtained in scenario was between £11,359 and £45,492 per QALY. The model is most sensitive to the assumptions regarding duration of treatment and the time horizon.

Results of scenario analysis were presented in Table 74 below.

Table 74: Results of scenario analysis

Scenario	Incremental cost with Palforzia	Incremental utility with Palforzia	ICER in comparison to avoidance alone
Base case	21,199	0.916	23,142
Scenario 1 – time horizon 5 years	9,628	0.227	42,447
Scenario 2 – time horizon 20 years	14,808	0.584	25,372
Scenario 3 - ARTEMIS	20,313	0.845	24,042
Scenario 4 – long-term outcomes [redacted]	39,440	0.867	45,492
Scenario 5 – long-term outcomes [redacted]	30,034	0.864	34,775
Scenario 6 – long-term outcomes [redacted]	15,826	0.991	15,966
Scenario 7 – long term outcomes [redacted]	11,662	1.027	11,359
Scenario 8 – utilities (Palforzia treated participants excluded)	21,199	0.798	26,550
Scenario 9 – utilities (interview sample only)	21,199	1.139	18,610
Scenario 10 – the same utilities in avoidance only arm across all states	21,199	0.986	21,500
Scenario 11 – 1 carer per child	21,199	0.838	25,308
Scenario 12 – 2 carers per child	21,199	0.929	22,824

3.8.4 Summary of sensitivity analyses results

Results of sensitivity analysis confirmed the base case results. The PSA results are similar to those of the base case. At a threshold of £30,000/QALY, the probability of Palforzia being cost-effective compared to avoidance is 64.4%. The model is sensitive to assumptions regarding utilities and long-term outcomes of Palforzia treatment. In the majority of scenarios and items tested in OWSA the ICER remains below £30,000/QALY.

B.3.9 Subgroup analysis

No sub-groups are presented in the model. As discussed in the Section B.2.7 and presented in Appendix E, no clinically meaningful sub-groups were identified within the Palforzia clinical trials.

B.3.10 Validation

3.10.1 Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation. The model protocol was developed internally by two independent health economists and checked for accuracy by another. Two clinical experts (one from UK and one from France) and a UK external expert health economist reviewed the approach and methodology proposed in the protocol, and provided suggestions for improvement which were implemented. In particular, the underlying assumptions, structure of the economic model, eligible population, comparators, and cost categories were ratified at the protocol stage.

Upon development of the first draft of the model, a face-to-face session was held with key stakeholders in the development of the model, a member of an Evidence Review Group and a quality-of-life expert. Clinical trial and economic data underpinning the model structure and assumptions were assessed by these experts.

The clinical inputs of the model were verified against the results published or reported from PALISADE, ARTEMIS and ARC004, whereby it was found that the clinical parameters closely reflected the reported outcomes of the studies.

Resource use and unit cost assumptions were discussed and validated with a UK clinical expert.

Additionally, model outcomes were validated against existing materials in the literature. Comparisons were drawn against the recent cost-effectiveness analysis of Palforzia performed by ICER-US. The review identified similar key cost-effectiveness drivers as those identified in this model. QALY gains are mostly driven by a reduction in anxiety and associated improvement in ability to fulfil normal daily activities. The reduced anxiety would arise from the knowledge that patients have higher tolerance to peanut protein, which in turn reduces the risk of an adverse reaction. In both the

ICER-US model and this model, this quality-of-life improvement is the main factor contributing to the higher number of QALYs accrued with Palforzia compared to avoidance.

The main cost driver, in line with the ICER-US report, is the cost of immunotherapy, as the overall associated disease management costs are low in comparison to other lifelong conditions. In summary, the main drivers identified in this model – i.e. health state quality of life improvements and therapy costs – tally with those in the ICER-US review of peanut allergy treatments.

Extrapolation of clinical outputs was validated against existing materials in the literature that reported the frequency of reactions. An economic model by Shaker 2018, et al. references a study by Vander Leek which reported that, over 5 years, 31 out of 53 patients with peanut allergy had at least one reaction caused by accidental exposure to peanut protein.[115] This would translate to approximately 11.7% of patients experiencing a reaction to peanut protein per year if reliant on avoidance alone. This compares well with the rate of reactions used in this model for patients relying on avoidance alone, in the tolerated dose of peanut protein <300 mg health state, where 9.3% of patients per year are conservatively estimated to experience a reaction. The annual 9.3% frequency was derived from PALISADE study patient clinical history.[122]

B.3.11 Interpretation and conclusions of economic evidence

The performed economic evaluation of Palforzia is based on the largest conducted to date clinical programme in peanut allergy, which included several centres in the UK.

The results from the base case analysis show that, over a lifetime horizon, **Palforzia** is associated with a **QALY gain** of **0.916** and incremental costs of **£21,199**, resulting in an **ICER of £23,142 per QALY gained**. The corresponding **probabilistic** result is **£25,011 per QALY** gained.

In interpreting the economic evaluation of Palforzia, the following points should be noted:

Utility and QALY gains were in line with the literature, previous economic models and Palforzia patient and caregiver feedback

- The results from the economic evaluation are consistent with the published economic literature. In the ICER-US report,[104] a 0.75 QALY gain was estimated for Palforzia in comparison to avoidance, which is lower than in the current cost-effectiveness analysis; however, disutility of carers was not included in the base-case in the ICER-US model. In the model presented within this submission, both patient and caregiver utility gain assumptions are in line with the assumptions used in the independent ICER-US model.
- Including both patient utility and carer disutility is consistent with findings from the recent literature, where substantial patient and carer burden of peanut allergy was found (see Section B.1.3.3). Additionally, the recent Danish study by Jacobsen et al. (2020)[51] estimated a lifetime DALY impact of 3.4 DALYs due to peanut allergy due to a significant disutility associated with peanut allergy and food allergy in general among children.
- Summing up, a mean gain of 0.916 QALYs over a patient's lifetime appears both reasonable and conservative, and also in line with strong positive feedback about the transformational benefits of treatment from patients and caregivers who participated in the Palforzia trials (see Section B.2.13 and Appendix P utility report for patient and caregiver feedback).

Resource use and costs associated with Palforzia administration and TRAEs were estimated conservatively, and relevant to UK clinical practice.

- Regarding Palforzia administration, up-dosing visit costs were conservatively assumed to cost £192 per visit, based on an allergy service outpatient visit NHS service cost, however a bottom-up costing of the estimated resources was around £108 per visit.
- In respect of TRAEs, these would be expected to reduce over time with continued treatment, however the model maintains them at rates seen in year 2 of treatment within the ARC004 study and no additional benefits were assumed beyond 2 years of treatment.
- Furthermore, resource use and cost inputs have been validated with a UK clinical expert to ensure the analysis is relevant to UK clinical practice and

settings. Accordingly, the main sources of unit cost data were: NHS reference costs 2018/2019[133], BNF[137] and NHS Ambulance Services report[139].

Palforzia appears cost-effective compared to peanut avoidance only, the current management strategy, allowing for uncertainty around long-term treatment outcomes

- Although there is uncertainty regarding treatment duration and long-term outcomes of Palforzia treatment, including rates of discontinuation, transition to regular inclusion of peanut in diet and to reversion to peanut avoidance only, which Aimmune endeavoured to reduce with the SHELF expert elicitation, Palforzia appears cost-effective at list price, with a good degree of certainty at £20,000-£30,000 per QALY as demonstrated in the probabilistic sensitivity analysis.

In conclusion, the analysis adopted a conservative approach to QALY gains and costs, and uncertainty of key long-term parameters has been incorporated based on a robust expert elicitation exercise. Based on this analysis, Palforzia represents a cost-effective use of NHS resources in England, providing life-changing benefits to children with peanut allergy and their families.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional clinical effectiveness data

Appendix M: FAQLQ and FAIM questionnaires

Appendix N: SHELF Elicitation study summary

Appendix O: Cost-effectiveness sensitivity analysis – inputs in the ARTEMIS scenario

Appendix P: Aimmune utility study report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal: Palforzia for treating peanut allergy [ID 1282]

Addendum to the company evidence submission documents

Aim:

The aim of the addendum is to update the documents A and B submitted for the single technology appraisal 'Palforzia for treating peanut allergy [ID 1282]' with a new Palforzia price and the resulting impact on the cost-effectiveness analysis.

Updates in the Document A:

- **Section The technology, Table 1: Technology being appraised – Document B, Section B.1.2 (page 11-12), page 7**

List price and average cost of a course of treatment	[redacted]

- **Section A13, Base-case ICER (deterministic), page 23**

Over the lifetime time horizon, treatment with Palforzia was associated with 20.000 QALYs at a cost of £31,742, and avoidance alone strategy accrued 19.084 QALYs at a cost of £11,973. This corresponds to 0.916 incremental QALYs at an incremental cost of £19,769 for Palforzia compared with avoidance. The incremental cost effectiveness ratio (ICER) for Palforzia compared to avoidance only is **£21,581** per QALY gained.

- **Section A13, Base-case ICER (deterministic), Table 2: Base-case results (deterministic) – Document B, Section B.3.7.1 (page 165), page 7**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	31,742	26.8	20.000	19,769	0.000	0.916	21,581
Avoidance only	11,973	26.8	19.084				

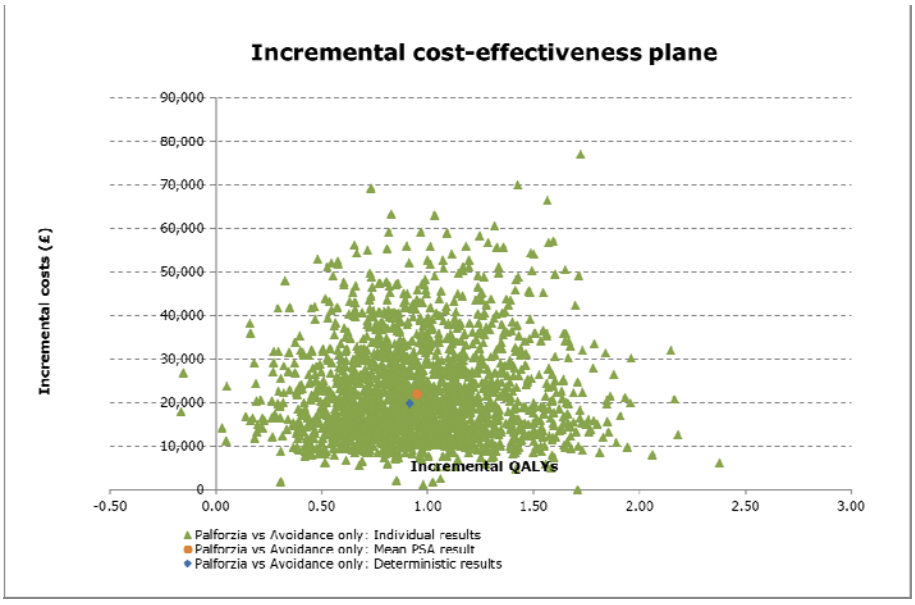
- **Section A14 Probabilistic sensitivity analysis, page 24**

The incremental cost-effectiveness plane (**Error! Reference source not found.**) shows that 99.87% of the iterations fell in the north east quadrant of the cost-effectiveness plane, where Palforzia is more costly and more effective.

- **Section A14 Probabilistic sensitivity analysis, Table 8: Base-case results (probabilistic) – Document B, Section B.3.8.1 (page 167), page 24**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,979	20.011	22,060	0.948	23,270
Avoidance only	11,919	19.063			

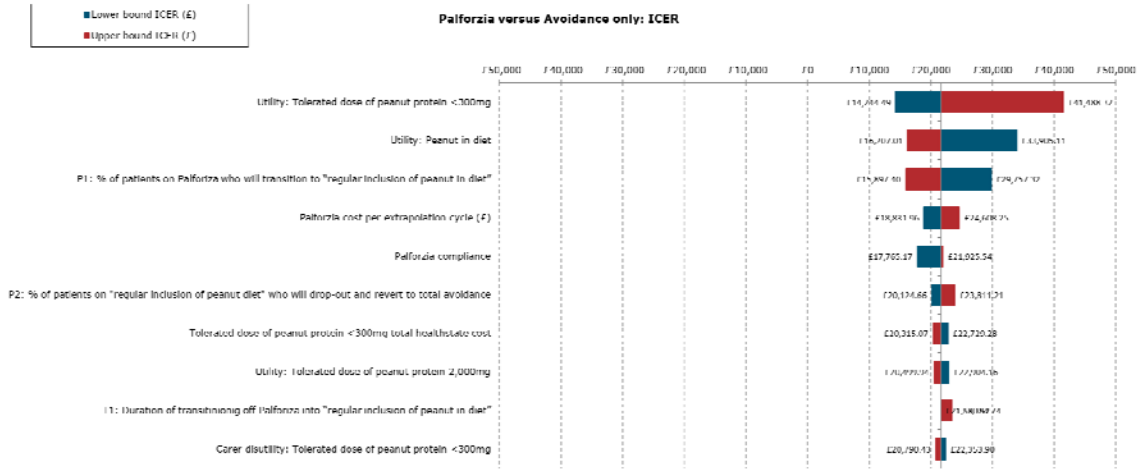
- **Section A14 Probabilistic sensitivity analysis, Figure 6: Incremental cost-effectiveness plane– Document B, Section B.3.8.1 (page 167), page 24**



- **Section A15 Key sensitivity and scenario analyses, Table 3: Ten main parameters included in the OWSA with the largest impact on results – Document B, Section B.3.8.2 (page 169), page 25**

Parameter	Base case value	Lower bound parameter	Upper bound parameter	Comment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- **Section A15 Key sensitivity and scenario analyses, Figure 1: OWSA Tornado diagram – Document B, Section B.3.8.3 (page 170), page 26**



- **Section A15 Key sensitivity and scenario analyses, page 26**

Results are most sensitive to the utility value associated with patients <300 mg tolerance health state where the lower bound produces an ICER of £14,244 and the upper bound produces an ICER of £41,488.

- **Section A15 Key sensitivity and scenario analyses, Table 4: Key scenario analyses – Document B, Section B.3.8.3 (page 170), page 26**

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (£)
Base case			**21,581**
Scenario 1 – time horizon 5 years	Time horizon	Given the variability of time horizons used in the literature, assessing the influence of different time horizons will allow a robust assessment of cost-effectiveness.	40,032
Scenario 2 – time horizon 20 years	Time horizon	Given the variability of time horizons used in the literature, assessing the influence of different time horizons will allow a robust assessment of cost-effectiveness.	23,756
Scenario 3 - ARTEMIS	Inputs from the ARTEMIS trial	Data from the ARTEMIS trial were used in the scenario analysis. Inputs are described in the Appendix O	22,404
Scenario 4 – long-term outcomes	[redacted]	Different assumptions regarding long-term outcomes were explored, including transition to consumption of peanut in diet (P1), reversion to avoidance only	42,163

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (£)
	[redacted]	(P2), and duration of such transitions (T1 and T2)	
Scenario 5 – long-term outcomes	[redacted]	as scenario 4	32,300
Scenario 6 – long-term outcomes	[redacted]	as scenario 4	14,960
Scenario 7 – long-term outcomes	[redacted]	as scenario 4	10,712
Scenario 8 – utilities (Palforzia-treated participants excluded)	Utilities pooled from the utility treatment naïve survey with results from Palforzia survey excluded	Utilities estimation has the biggest impact on results (see OWSA). Impact of different utilities assumptions were investigated.	24,758
Scenario 9 – utilities (interview sample only)	Utilities from the interviews only	as scenario 8	17,354
Scenario 10 – the same utilities in avoidance only arm across all states	The same utility across all health states in the avoidance arm (as in the <300 mg tolerated dose health state)	In real life, patients following an avoidance only strategy would not experience the disutility of up-dosing, but equally the small percentage of avoidance arm patients who tolerated ≥300mg in the PALISADE exit DBPCFC would not have been aware in real-life, hence would not have experienced associated utility gains.	20,627
Scenario 11 – 1 carer per child	1 carer	There is limited evidence to support the number of patients caring for patients with peanut allergy, therefore the base-case assumption is varied.	23,601
Scenario 12 – 2 carers per child	2 carers	as scenario 11	21,284

Updates in the Document B:

- **Section B.1.2 Description of the technology being appraised, Table 2 Technology being appraised, page 12:**

List price and average cost of a course of treatment	[redacted]

- **Section B.3 Cost-effectiveness, page 104**

- A Markov model based on different peanut protein tolerance health states and data from the Palforzia pivotal trials was used to evaluate the cost-effectiveness of Palforzia for patients with peanut allergy.
- A cost-effectiveness analysis was conducted to compare Palforzia (in combination with avoidance) versus avoidance alone.
- In base case analyses Palforzia was cost-effective versus avoidance, with an incremental cost-effectiveness ratio (ICER) of **£21,581 per QALY**.
- Deterministic sensitivity analyses demonstrated that the cost-effectiveness results were robust to changes in model parameters, with the majority of scenarios remaining cost-effective, and ICERs remaining <£30,000 per QALY (range £14,244 – £41,488 per QALY).
- In probabilistic sensitivity analysis there was a 42.87% probability of Palforzia being cost-effective versus avoidance at a willingness-to-pay threshold of £20,000 per QALY, and **a 68.64% probability** of Palforzia being cost-effective versus avoidance at a willingness-to-pay threshold of **£30,000 per QALY.**
- Palforzia remained cost-effective in scenario analyses which varied key model parameters, with the majority of scenario analyses resulting in ICERs <£30,000 per QALY.
- Consequently, Palforzia is likely to be a cost-effective use of NHS resources for the treatment of peanut allergy.

- **Section 3.5.1 Palforzia – drug and administration costs, page 148, first sentence in the section:**

A [redacted] per day was applied for each dose of Palforzia (range 0.5–300 mg), consequently any dose reduction does not impact on the cost.

- **Section 3.5.1 Palforzia – drug and administration costs, Table 61 Drug costs per day, page 148**

Intervention	Daily drug cost	Compliance
Palforzia	[redacted]	[redacted]
Avoidance	£0	Not relevant
Peanuts in diet	£0	Not relevant

- **Section 3.5.1 Palforzia – drug and administration costs, Table 63 Total Palforzia drug cost per cycle, page 150**

Cycle	Acquisition costs per cycle (£)	Administration cost per cycle (£)	Total cost per cycle (£)
Up-dosing, First cycle - Initial escalation dose (duration: 1 day)	[redacted]	485	[redacted]
Up-dosing, next cycles (duration: 14 days)	[redacted]	192	[redacted]
Maintenance (duration: 28 days)	[redacted]	0	[redacted]
Extrapolation (duration: 1 year)	[redacted]	0	[redacted]

- **Section 3.6.1 Summary of base-case analysis inputs, Table 68 Summary of variables applied in the economic model, page 163**

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Costs			
Daily cost of Palforzia	[redacted]	Gamma distribution calculated separately for each treatment phase by using SE=10% of mean	Section B.3.5.1

- **Section 3.7.1 Base-case incremental cost-effectiveness analysis results, page 165**

Aggregated base case results for the cost-effectiveness of Palforzia compared to avoidance are presented in **Error! Reference source not found.**. Over the lifetime time horizon, treatment with Palforzia was associated with 20.000 QALYs at a cost of £31,742, and avoidance alone strategy accrued 19.084 QALYs at a cost of £11,973. This corresponds to 0.916 incremental QALYs at an incremental cost of £19,769 for Palforzia compared with avoidance. The ICER for Palforzia compared with avoidance only is £21,581 per QALY gained.

- **Section 3.7.1 Base-case incremental cost-effectiveness analysis results, Table 5: Base-case results, page 165**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	31,742	26.8	20.000	19,769	0.000	0.916	21,581
Avoidance only	11,973	26.8	19.084				

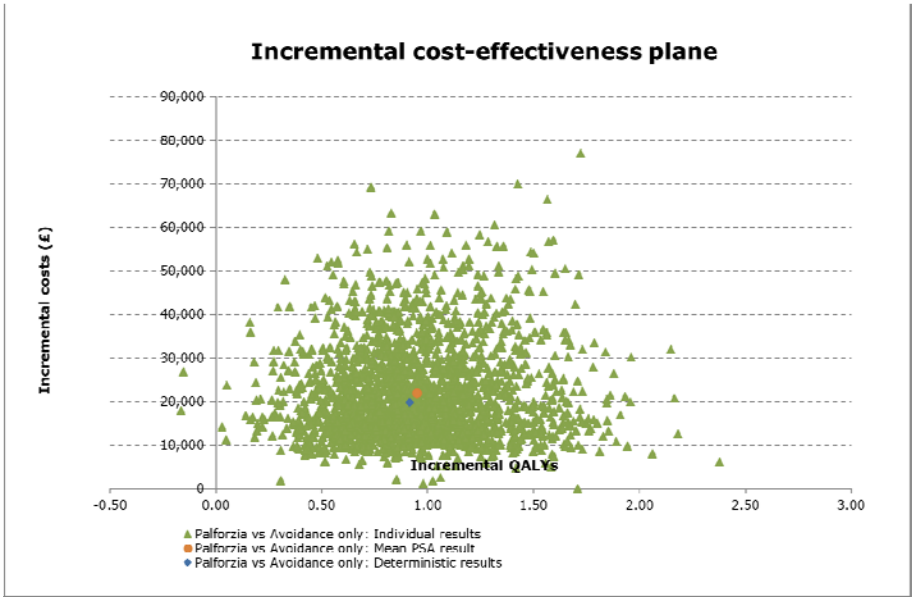
- **Section 3.8.1 Probabilistic sensitivity analysis, page 166 and 167**

Table 6 shows the mean results of the PSA. Results are similar to that of the base case. The incremental cost-effectiveness plane (Figure 2) shows that 99.87% of the iterations fell in the north east quadrant where Palforzia is more costly and more effective. The CEAC, as presented in Figure 3, illustrates the probability of Palforzia being cost-effective compared to avoidance, at various willingness to pay thresholds. At thresholds of £20,000/QALY and £30,000/QALY, the probability of Palforzia being cost-effective compared to avoidance is 42.87% and 68.64% respectively.

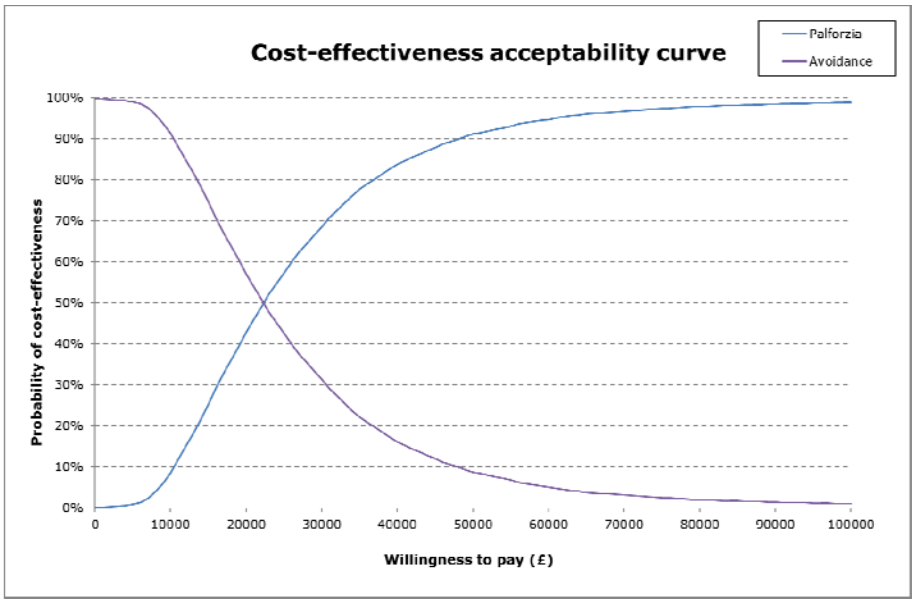
- **Section 3.8.1 Probabilistic sensitivity analysis, Table 6: PSA results, page 167**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,979	20.011	22,060	0.948	23,270
Avoidance only	11,919	19.063			

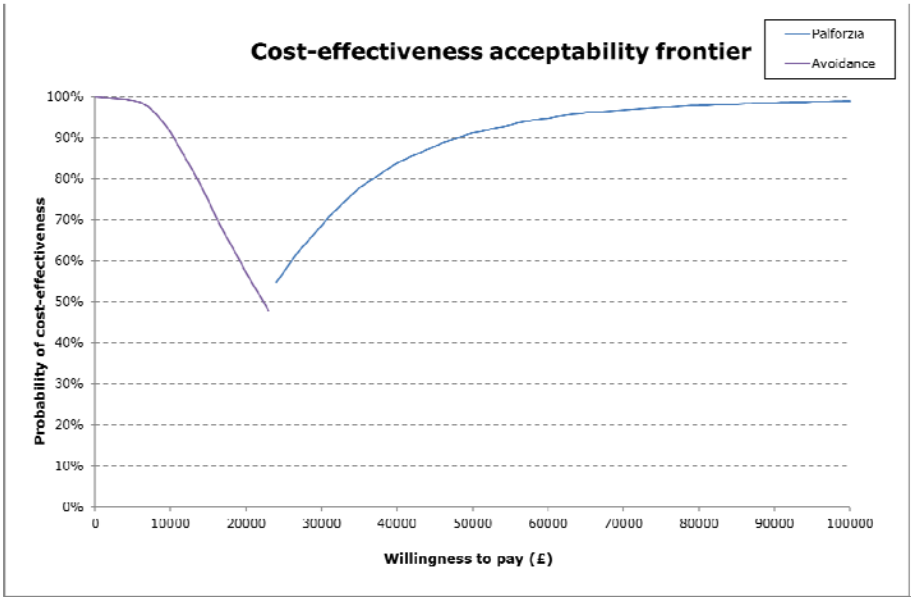
- **Section 3.8.1 Probabilistic sensitivity analysis, Figure 2: Incremental cost-effectiveness plane, page 167**



- **Section 3.8.1 Probabilistic sensitivity analysis, Figure 3: Cost-effectiveness acceptability curve, page 168**



- **Section 3.8.1 Probabilistic sensitivity analysis, Figure 4: Cost-effectiveness acceptability frontier, page 168**



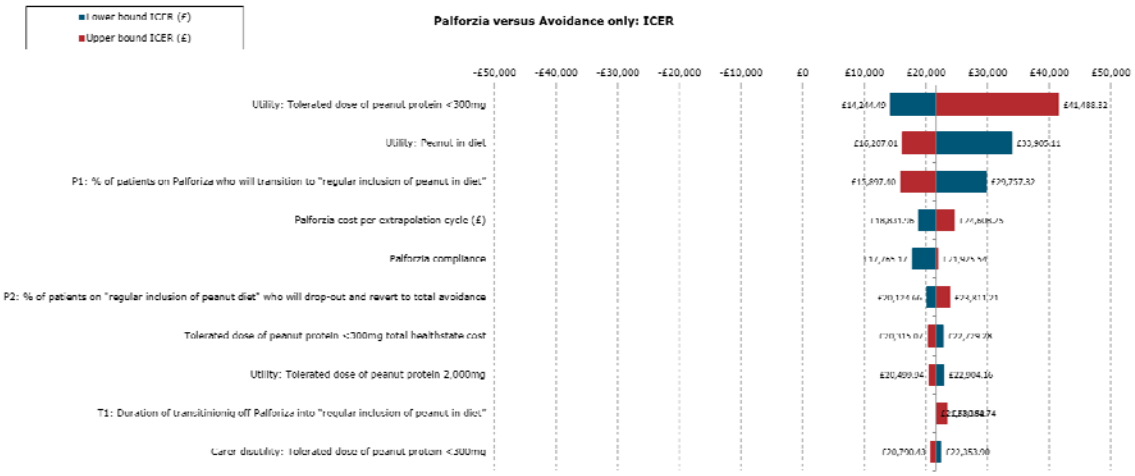
- **Section 3.8.2 Deterministic sensitivity analysis, Table 7: Ten main parameters included in the OWSA with the largest impact on results, page 169**

Parameter	Base case value	Lower bound parameter	Upper bound parameter	Comment
Palforzia cost per extrapolation cycle (£)	[redacted]	[redacted]	[redacted]	[redacted]

- **Section 3.8.2 Deterministic sensitivity analysis, page 170**

Results are most sensitive to the utility value associated with patients <300 mg tolerance health state where the lower bound produces an ICER of £14,244 and the upper bound produces an ICER of £41,488.

- **Section 3.8.2 Deterministic sensitivity analysis, Figure 5: OWSA tornado diagram, page 170**



- **Section 3.8.3 Scenario analysis, page 172**

The ICER range obtained in scenarios was between £10,712 and £42,163 per QALY.

- **Section 3.8.3 Scenario analysis, Table 8: Results of scenario analysis, page 173**

Scenario	Incremental cost with Palforzia	Incremental utility with Palforzia	ICER in comparison to avoidance alone
Base case	19,769	0.916	21,581
Scenario 1 – time horizon 5 years	9,081	0.227	40,032
Scenario 2 – time horizon 20 years	13,865	0.584	23,756
Scenario 3 - ARTEMIS	18,927	0.845	22,404
Scenario 4 – long-term outcomes [redacted]	36,554	0.867	42,163
Scenario 5 – long-term outcomes [redacted]	27,896	0.864	32,300
Scenario 6 – long-term outcomes [redacted]	14,829	0.991	14,960
Scenario 7 – long term outcomes [redacted]	10,998	1.027	10,712

Scenario	Incremental cost with Palforzia	Incremental utility with Palforzia	ICER in comparison to avoidance alone
[redacted]			
Scenario 8 – utilities (Palforzia treated participants excluded)	19,769	0.798	24,758
Scenario 9 – utilities (interview sample only)	19,769	1.139	17,354
Scenario 10 – the same utilities in avoidance only arm across all states	19,769	0.958	20,627
Scenario 11 – 1 carer per child	19,769	0.838	23,601
Scenario 12 – 2 carers per child	19,769	0.929	21,284

- **Section 3.8.4 Summary of sensitivity analyses results, page 173**

At a threshold of £30,000/QALY, the probability of Palforzia being cost-effective compared to avoidance is 68.64%.

- **Section B.3.11 Interpretation and conclusions of economic evidence, page 175**

The results from the base case analysis show that, over a lifetime horizon, **Palforzia** is associated with a **QALY gain** of **0.916** and incremental costs of **£19,769**, resulting in an **ICER of £21,581 per QALY gained**. The corresponding **probabilistic** result is **£23,270 per QALY** gained.

Updates in the Appendix J:

- **Section J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis, Table 9: Costs by health state, page 164**

Health state	Up dosing	Treatment maintenance	Tolerated dose of peanut protein <300 mg	Tolerated dose of peanut protein 300 mg	Tolerated dose of peanut protein 600 mg	Tolerated dose of peanut protein 1000 mg	Tolerated dose of peanut protein 2000 mg	Spontaneous tolerance	Peanut in diet	Total QALYs
Palforzia	4,249	1,629	4,873	1,321	1,450	5,329	7,368	0	5,523	31,742
Avoidance only	194	213	10,655	457	183	273	0	0	0	11,973
Incremental costs of Palforzia	4,055	1,416	-5,782	864	1,268	5,057	7,368	0	5,523	19,769
Absolute incremental costs of Palforzia	4,055	1,416	5,782	864	1,268	5,057	7,368	0	5,523	19,769
Percentage of total incremental costs of Palforzia	21%	7%	-29%	4%	6%	26%	37%	0%	28%	100%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palforzia for treating peanut allergy [ID1282]

Clarification questions

June 2021

File name	Version	Contains confidential information	Date
ID1282 Palforzia clarification letter from ERG to NICE Aimmune response 300621.doc	1	Yes	30 June 2021

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Document B, Section B.2.2. The company submission states that RAMSES (ARC007) and the respective open label extension study ARC011 were excluded since they only assessed safety and tolerability, not efficacy, and were conducted only in the United States. It also states that ARC001 and its open-label extension ARC002 were not included in the cost-effectiveness model or the SmPC since both trials were Phase 2, relatively small and only conducted in the US. Given that the subgroup analyses are performed by North America and Europe geographical regions, please clarify the reasons for excluding these trials based on their location in the US.

RAMSES (ARC007) and the respective open label extension study ARC011 were primarily excluded due to the lack of efficacy endpoints i.e. food challenges in the RAMSES study, and the small size of ARC001 (n=55 patients).

Please note however that RAMSES study safety results have been pooled with ARTEMIS and PALISADE and presented in the safety section of the company submission document (Section B.2.10.3, page 96).

The location of the studies in the US was a further point of context regarding generalisability of the studies for the UK but was not the main reason for exclusion. A copy of the clinical study report (CSR) for RAMSES is provided alongside this response. Please note that this is provided as AiC as the study has yet to be published. The publications for ARC001 and its open-label extension ARC002 are also provided (Bird et al., 2018[1], Bird et al. 2018[2,3]).

Methods used to assess the clinical effectiveness evidence

A2. Appendix D, Section D1.2 Please clarify how many reviewers conducted full text screening and whether reviewers worked independently.

Two independent reviewers conducted the full text screening.

A3. Document B, Section B.2.5 and Appendix D, Section D1.4. Please clarify whether the quality assessment was conducted by two or more reviewers, and whether the reviewers worked independently.

Two independent reviewers conducted the quality assessment.

A4. Document B, Section B2.8 Please clarify whether a meta-analysis including some or all of the following studies (PALISADE, ARTEMIS, ARC001) was attempted; if so, please provide full details of the methodology and results of this analysis.

No pairwise meta-analysis between any of PALISADE, ARTEMIS and ARC001 has been conducted. The decision not to conduct a pairwise meta-analysis was preceded by an assessment of study heterogeneity. Significant heterogeneity among the studies highlighted the fact that a meta-analysis was simply not feasible (Company Submission Table 23, Section B.2.8., page 92) and that the results would be biased and misleading.

Pooling PALISADE and ARTEMIS data at a patient level was also discounted, primarily due to the different lengths of the maintenance periods across the studies. As mentioned in the company submission document (Section B.2.8, page 92), the

rationale and decision not to pool the studies for efficacy was accepted by both the EMA and FDA.

Nevertheless, for safety assessment pooling the data was justified, as this provided additional insight on the serious adverse events rates, which were rare and therefore easier to capture in a large cohort of patients.

A network meta-analysis (NMA), which included PALISADE and non-Aimmune studies investigating Viaskin-Peanut, oral immunotherapy and sublingual immunotherapy was attempted but not finalised by Aimmune due to significant heterogeneity of methodology, inclusion criteria and endpoints between trials meaning that a robust analysis could not be conducted. As such no finalised report of methodology or results is available or planned to be developed. It is important to note that Institute for Clinical and Economic Review agreed that an NMA would have been inappropriate due to differences of trial design.

Adverse events

A5. PRIORITY. Document B, Section B.2.2. The submission indicates that RAMSES (ARC007) and the respective open label extension study ARC011 were excluded since they only assessed safety and tolerability, not efficacy, and were conducted exclusively in the United States (US); however, on page 98 of the CS, it is reported that a submitted manuscript, which is currently under review, included the [redacted]. Please clarify what type of safety and tolerability data were reported in RAMSES, and whether any adverse event and treatment-related adverse event data were collected in RAMSES. If available, please provide the trial report for the RAMSES study only (not the RAMSES data combined with the other studies).

RAMSES (ARC007) was a multicentre, randomised, double-blind, placebo-controlled Phase 3 study evaluating the safety and tolerability of Palforzia in North America (US and Canada). The primary endpoint was the frequency of treatment-emergent adverse events (TEAEs), including serious adverse events. RAMSES gathered and reported the same safety and tolerability outcomes as in the two main pivotal trials

PALISADE and ARTEMIS. As mentioned above a copy of the CSR for RAMSES is provided (as AiC) alongside this response.

A6. Document B, Section 2.10.2. The company submission states "*Treatment-related adverse events (TRAEs) are a subset of TEAEs related specifically to treatment as determined by the investigator*". Please clarify the definition of TRAEs; in particular, what constitutes a TRAE and how this was determined by the investigator.

Treatment-emergent adverse events (TEAEs) are defined as those adverse events with onset after the first dose of the study intervention; these adverse events may or may not be related to the study intervention.

Treatment-related adverse events (TRAEs) are those deemed by the study investigator to be related to the study intervention and are a subset of all-cause treatment-emergent adverse events occurring during the study.

The determination of whether a TEAE qualifies as a TRAE is the opinion of the investigator based on their clinical judgement and expertise as a trained allergist. At the point the determination is made, the investigator is still blinded to whether the subject has taken active product or placebo. It is expected in the patients in the active arm of the studies that they will experience AEs that are related to treatment, given that Palforzia contains the allergen, they are allergic too. It should be noted that TRAEs reduce over time with continued treatment.

Section B: Clarification on cost-effectiveness data

Model structure

B1. PRIORITY. Document B, Section 3.2.8; Figures 24-25; page 114. Please provide further justification for the decision to split the tolerance health states based on the MTD, specifically describing what differences in resource use and quality of life may be expected between the different degrees of tolerance in routine practice. The ERG notes that the ICER evaluation combined the response health states,

which would appear to be more consistent with the primary outcome for the trial. The decision to split the tolerance states adds further uncertainty due to small numbers of transition events informing some of the transition probabilities, particularly in the period from years 1 to 2. Please provide a scenario where all the model parameters are set equal across the tolerance health states, with data for combined tolerance health states obtained from the trial where possible.

Aimmune considers there to be a difference between tolerance health states in terms of resource use and quality of life. The evidence suggests that there is a trend towards improving quality of life and decreasing AEs/anaphylaxis rates with improvement of the maximum tolerated dose (MTD) of peanut protein. The integrated safety analysis shows that mild to moderate TRAEs were often experienced early in treatment, but both incidence and severity of TRAEs declined with prolonged treatment and with higher tolerance of peanut protein (Company Submission, Section B2.10.3, page 98, Figure 22). The risk quantification study estimates that there is around an 88% reduction in the number of accidental exposure reactions to peanuts when patients move from <300mg MTD to 300mg MTD and around a 97% reduction when patients move to 600 mg or a higher tolerated dose of peanut protein (Company Submission, Section B2.10.3, page 129, Table 36). Decrease in severity and frequency of TRAEs, as well as reduction in accidental exposure rates will lead to differences in quality of life and the resources associated with treating these events.

The requested scenario analysis where all the model parameters are set equal across the tolerance health states has been conducted. The changes made to the base case scenario are presented in the table below (Note: all other model parameters remained the same as in the base case).

Please note that in line with the request above to use data from the clinical trials where possible, and in line with question B6, we have replaced probabilities of accidental exposures from the risk quantification study with accidental exposure data from the trials.

Variable	Value	Comment/Reference
Utilities		
Utility for all tolerance health states: 300 mg, 600 mg, 1000 mg, 2000 mg	0.859	Utility for 'Tolerate 6-8 peanuts/Current' health state (Company submission, section 3.4.4)
Accidental exposures to peanuts		
Up-dosing and maintenance: accidental exposures requiring treatment and accidental exposures requiring adrenaline	Company submission, Table 34, page 128	The same as in the base case
<300 mg	Annual rate: 9.95% – accidental exposures requiring treatment Annual rate: 2.3% – accidental exposure requiring adrenaline	Calculated based on the number of accidental exposures requiring treatment that were observed in the placebo group of the PALISADE trial (13 events out of 124 patients – Hourihane et al 2019), converted to annual probabilities. 23% (3/13) of exposures that required treatment also required adrenaline (Hourihane et al 2019).
300, 600, 1000, 2000 mg MTD	Annual rate: 9.59% – accidental exposures requiring treatment Annual rate: 3.53% – accidental exposure requiring adrenaline	Calculated based on ARC004 results in cohorts 1 and 3A, combined and adjusted to include different durations of treatment in both cohorts (ARC004, CSR, Table 63 and Table 14.3.7.6) Rates in Cohort 1 (109 patients): 8 events of accidental exposures related to peanuts, 73% of patients with accidental exposure required treatment, 26% required adrenaline. Rates in Cohort 3A (31 patients): 8 events of accidental exposures related to peanuts, 43% of patients with accidental exposures required treatment, 14% required adrenaline.
Treatment-related anaphylactic reactions		
300, 600, 1000, 2000 mg MTD	Annual probability of mild reaction: 10.27% Annual probability of moderate reaction: 7.47%	The same for all health states, average across 600 and 1000 mg MTD health states reported in ARC004, 300mg population too small to observe reactions.
Non-anaphylactic TRAEs		
300, 600, 1000, 2000 mg MTD	0% for all non-anaphylactic TRAEs	The same for all health states, Company submission, Table 47, page 136

Results of the scenario are presented in the table below. With all parameters set equal across tolerance health states, the ICER for Palforzia compared with avoidance only is £23,751 per QALY gained compared to £23,142 per QALY for the base case.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,769	26.8	20.045	21,484	0.000	0.905	23,751
Avoidance only	12,285	26.8	19.140				

B2. Document B, Section 3.2.8; Figures 24-25; page 114. Please comment further on the validity of the assumption that the MTD cannot change in the avoidance arm over time. What biases (if any) might this introduce for the assessment of cost-effectiveness. What is the validity of this assumption?

In the avoidance arm MTD can change in the first year of treatment. This is in line with PALISADE and ARTEMIS results for the placebo arm at the exit food challenge. It was assumed that thereafter patients will remain at the level of sensitivity observed in the exit food challenge for the remainder of the model. Aimmune considers this to be a valid assumption.

Clinical opinion and current literature estimate that up to 20% of people with PA will grow out of their disease and become peanut tolerant around the age of 5 years (Company submission, Section 1.3.1, page 17). The Palforzia pivotal studies include patients from the age of 4, so it is possible that some of these patients would still grow out of their PA and tolerate peanuts. To account for this, the model assumes that 5% of patients on both Palforzia and avoidance arms will move to the spontaneous tolerance health state over their lifetime. This assumption was discussed and validated with 8 UK clinical experts, following the SHELF elicitation exercise (Company submission, Appendix N, page 218). The model user can vary this assumption in order to see the impact on the cost-effectiveness results. It is however important to note that in real life, even if someone with PA did become

spontaneously tolerant, they may not be aware of it until they either had an accidental exposure or a food challenge and didn't react.

Clinical parameters and variables

B3. Section B.3.3.4. Treatment related anaphylactic reactions. The decision to exclude severe anaphylactic reactions because they are rare, and only include mild and moderate reactions (also quite rare), does not seem well justified. Please provide a scenario analysis where all treatment related anaphylactic reactions are included in the model and disaggregated by severity based on the proportional distribution of mild, moderate, and severe events in the different treatment phases of trial.

There was only one case of severe anaphylactic reaction reported in the PALISADE trial (during maintenance), [redacted] case in ARC004 daily dosing cohorts and no cases in ARTEMIS (Company Submission, Section B3.3, page 119).
The scenario with all anaphylactic reactions included has been created with the following frequency and probability of anaphylactic reactions assumed.

Variable	Value	Comment/Reference
Inputs for mild anaphylactic reaction	The same as in the base case	
Inputs for moderate anaphylactic reaction	The same as in the base case	
Severe anaphylactic reaction frequency in Palforzia health states:		
Up-dosing	0%	No cases in the PALISADE
Maintenance	0.05% per cycle (4 weeks)	1 case out of 310 patients over 25 weeks in the PALISADE
<300 mg MTD	0%	Assumption: no treatment-related anaphylactic reaction since patients in this state discontinue Palforzia
300 mg 600 mg 1000 mg 2000 mg	[redacted] per cycle (1 year)	[redacted] case out of 109 patients in Cohort 1 and [redacted] cases out of 30 patients in Cohort 3A, Note: duration of treatment in Cohort 1 – 28 weeks, Cohort 3A – 56 weeks
Severe anaphylactic reaction cost	£731.19	Assumed to be the same as cost of adverse reaction to accidental exposure to peanut protein requiring treatment with adrenaline
Severe anaphylactic reaction disutility	0.09	Assumed to be the same as disutility of adverse reaction to accidental exposure to peanut protein requiring treatment with adrenaline

Results of the scenario are presented in the table below. With inclusion of severe anaphylaxis, the ICER for Palforzia compared with avoidance only is £23,304 per QALY gained compared to £23,142 per QALY for the base case.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,319	26.8	20.000	21,346	0.000	0.916	23,304
Avoidance only	11,973	26.8	19.084				

B4. Document B, Section B, page 121. Treatment related adverse events.

Please provide the following:

a) full breakdown of the numbers of non-anaphylactic treatment related adverse events by organ system and severity as observed in the trials used to inform the model;

b) scenario that includes all TRAEs that have significant resource or utility implications, including during the long-term extrapolation using data from ARC004.

a) The breakdown of the numbers of non-anaphylactic TRAEs by organ system and severity that occurred in ≥5% in at least one arm of the study population was presented in Table 44 of the company submission document (Company submission, Table 44, page 135 - PALISADE) and Appendix O (Table 79, page 231 – ARTEMIS).

   Please find below tables with all TRAEs included, including those with lower incidence than 5% (anaphylactic reactions and accidental exposures are excluded, since they were included in the model separately).

PALISADE				
Adverse event	**Treatment up-dosing including IDE**		**Maintenance**	
	Palforzia (N=366)	Avoidance only (N=123)	Palforzia (N=310)	Avoidance only (N=118)
Moderate TRAEs (number of events)				
Moderate gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Other moderate TRAEs occurring in under 5% pts	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Severe TRAEs (number of events)				
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARC003 Clinical Study Report and patient level data analysis

ARTEMIS				
Adverse event	**Treatment up-dosing including IDE**		**Maintenance**	
	Palforzia (N=132)	Avoidance only (N=43)	Palforzia (N=108)	Avoidance only (N=41)
Moderate TRAEs (number of events)				
Moderate gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Moderate skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Other moderate TRAEs occurring in under 5% pts	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Severe TRAEs (number of events)				
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARTEMIS CSR and PLD

ARC004		
TRAE by organ system	Cohort 1 (n=109)	Cohort 3A (n=31)
Moderate TRAE by organ system		
Eye	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Total	[redacted]	[redacted]
Severe TRAE by organ system		
Total	[redacted]	[redacted]

Source: ARC004 CSR and PLD

a) The scenario with all moderate and severe TRAEs has been conducted. Mild TRAEs were not considered since they were considered not to have a significant impact on costs and utilities (Company submission, Section B.3.3, page 118), as confirmed by the clinical expert.

Rates of moderate and severe TRAEs as well as costs and disutility inputs used in the scenario are presented in the table below.

All moderate TRAEs regardless of organ system were combined for model purposes as, based on expert opinion, they were deemed to have the same cost and quality of life implications. The same approach was applied to severe TRAEs.

Variable	Value	Comment/Reference
Probability of moderate TRAEs		
Up-dosing, Palforzia, moderate TRAEs	10.04% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Up-dosing, avoidance, moderate TRAEs	1.69% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Maintenance, Palforzia, moderate TRAEs	3.90% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Maintenance, avoidance, moderate TRAEs	1.21% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
<300 mg, Palforzia moderate TRAEs	0% per cycle	Assumption (patients discontinue Palforzia and go to avoidance
<300 mg, avoidance, moderate TRAEs	0% per cycle	Assumption (no AEs related to treatment on avoidance)
300, 600, 1000 mg, 2000 mg Palforzia, moderate TRAEs	24.4% per cycle (year), the same for all health states	Calculated based on total number of [redacted] events in Cohort 1 and 3A in the ARC004
300, 600, 1000 mg, 2000 mg avoidance, moderate TRAEs	0% per cycle	Assumption (no AEs related to treatment on avoidance)
Probability of severe TRAEs		
Up-dosing, Palforzia, severe TRAEs	0.17% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Up-dosing, avoidance, severe TRAEs	0% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Maintenance, Palforzia, severe TRAEs	0.36% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
Maintenance, avoidance, severe TRAEs	0% per cycle	Calculated based on total number of [redacted] events from the PALISADE trial
<300 mg, Palforzia severe TRAEs	0% per cycle	Assumption (patients discontinue Palforzia and go to avoidance
<300 mg, avoidance, severe TRAEs	0% per cycle	Assumption (no AEs related to treatment on avoidance)
300, 600, 1000 mg, 2000 mg Palforzia, severe TRAEs	0% per cycle (year), the same for all health states	No events in Cohort 1 and 3A in the ARC004

Variable	Value	Comment/Reference
Probability of moderate TRAEs		
300, 600, 1000 mg, 2000 mg avoidance, severe TRAEs	0% per cycle	Assumption (no AEs related to treatment on avoidance)
Costs		
Moderate TRAEs	£14.52 per event	Company submission, section 3.5.6
Severe TRAEs	£731.19	Assumption, the same as Anaphylactic reaction requiring adrenaline, Company submission, section 3.5.5
Utilities		
Moderate TRAEs	0.07	Company submission, section 3.4.6
Severe TRAEs	0.09	Assumption, the same as Anaphylactic reaction requiring adrenaline, Company submission, section 3.4.6

Results of the scenario are presented in the table below. With inclusion of all moderate and all severe non-anaphylactic TRAES, the ICER for Palforzia compared with avoidance only is £23,247 per QALY gained compared to £23,142 per QALY for the base case.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,253	26.8	19.999	21,280	0.000	0.915	23,247
Avoidance only	11,973	26.8	19.084				

B5. Document B, Tables 34-37, page 127-131. Risk quantification study for risk of accidental exposure. Please provide full details of the approach and data used to derive the long-term risk of accidental exposure to peanuts from the risk quantification study. The ERG is currently unable to reproduce the data from Tables 34-37 and would appreciate full details of the approach used, including risk equations where appropriate for all parameters. If such information is available from the economic model file, please clarify where this information can be found.

The methods and technical details about calculations made in the risk quantification study are described in the following papers (provided alongside this response):

- Yu et al 2021(please find attached the updated version of the manuscript which has now been accepted by the journal *Advances in Therapy*),
- Supplemental materials to the Yu et al study,

- Taylor et al, 2009 and Remington et al, 2019 - prior studies that have quantified the risk reduction associated with immunotherapy for peanut-allergic patients and used similar methods.

In the cost-effectiveness model submitted by Aimmune, accidental exposure to peanuts was estimated as follows:

- Up-dosing and maintenance:
    - For up-dosing and maintenance, rates from the PALISADE trial were used (Company submission, Table 33, page 127).
    - The rates of the reactions that occurred over the study periods were converted into per-cycle probabilities (up-dosing: mean duration in the PALISADE trial – 22 weeks, model cycle duration: 2 weeks; maintenance: mean duration in the PALISADE trial – 25 weeks, model cycle duration: 4 weeks). The per cycle probabilities of anaphylactic reaction were presented in Table 34 of the Company submission (Company submission, Table 34, page 128). Exact formulas can be found in the Excel model in the sheet 'Data store' cells E481:F483 (Palforzia) and P481:Q483 (avoidance/placebo).
- <300mg MTD:
    - The value of 9.79% from the risk quantification study was used as a risk of accidental exposure to peanuts requiring treatment for patients in the <300 mg MTD health state (Company submission, Table 35, page 129).
    - This value was adjusted and converted to probability by a formula from Briggs et al: $p = 1 - e^{-\frac{r}{t}}$. The obtained rate 9.33% was used as a mean annual probability of accidental exposure reaction requiring treatment (Company submission, Section 3.3.3, page 129).
    - It was assumed that 3 out of 37 reactions requiring treatment would require adrenaline use (based on data from the PALISADE trial, Company submission, Section 3.3.3, page 130).
    - The exact formulas can be found in the excel model in the sheet 'Data store' cells G481:G483.

- 300 mg:
    - Based on the risk quantification study it was assumed that patients who will achieve 300mg MTD will have 88.37% reduction in the probability of having accidental exposure to peanut requiring treatment in comparison to patients in <300 mg MTD health state (Company submission, Table 36, page 129)
    - It was assumed that 3 out of 37 reactions requiring treatment would require adrenaline use (based on data from the PALISADE trial, Company submission, Section 3.3.3, page 130).
    - The exact formulas can be found in the excel model in the sheet 'Data store' cells H481:H483.
- 600 mg and 1000 mg
    - Based on the risk quantification study it was assumed that patients who will achieve 600mg MTD or 1000mg MTD will have 97.08% reduction in the probability of having accidental exposure to peanut requiring treatment in comparison to patients in <300 mg MTD health state (Company submission, Table 36, page 129)
    - It was assumed that 3 out of 37 reactions requiring treatment would require adrenaline use (based on data from the PALISADE trial, Company submission, Section 3.3.3, page 130).
    - The exact formulas can be found in the excel model in the sheet 'Data store' cells I481:J483.
- 2000 mg MTD: due to lack of data, the same values as for 1000 mg MTD were assumed.

B6. Document B, Tables 34-37, pages 127–131. Risk quantification study for risk of accidental exposure. Please clarify why, for year one onwards, rarity of events is considered a justification for precluding the use of trial data to populate the economic model. Linked to query B1 above, please explain whether it would have been possible to use data directly from the trial if the different tolerance states had been combined. Please provide these data for the combined tolerance states from the ARC004 study for the period between years 1 and 2 and apply a scenario

analysis that extrapolates these data forwards in all “tolerance” health states (as opposed to using the risk-quantification study data).

Accidental exposures to peanuts are relatively uncommon, with an annual incidence of around 10% or less (Company submission, Section 2.6.1, page 70 and Section 3.3.3, Table 33 (PALISADE); Section 2.6.3, page 77 (ARTEMIS)). The ARC004 study, with a combined sample size of only n=143 in the once daily dosing cohorts and a duration of only 28 weeks for most patients, was not intended to assess rates of real-world accidental exposures to peanuts, although these data were collected (there were 8 accidental exposures related to peanuts in Cohort 1 and 8 in cohort 3A, respectively; 73% of them in Cohort 1 and 43% in Cohort 3A required treatment. None were deemed serious). For reasons of sample size and a lack of control arm, the risk quantification study based on PALISADE patient data and clinical history was considered a more robust basis for estimating rates of accidental exposures for the model than data from the ARC004 trial.

However, as requested the following scenario analysis for accidental exposures rates has been conducted:

- Up-dosing and maintenance – data from the PALISADE trial used,
- <300mg MTD – frequency of accidental exposure was assumed to be the same as in the placebo arm in the PALISADE trial
- 300mg, 600 mg, 1000 mg, 2000 mg MTD health states - combined data for all accidental exposures occurred in the ARC004 study (Cohort 1 and 3A), the same rates for all health states.

The rates for accidental exposures used in the scenario are presented in the table below.

Accidental exposures related to peanuts	**Value**	**Comment/Reference**
Up-dosing and maintenance: accidental exposures requiring treatment and accidental exposures requiring adrenaline	Company submission, Table 34, page 128	The same as in the base case

Accidental exposures related to peanuts	Value	Comment/Reference
<300 mg	Annual rate: 9.95% – accidental exposures requiring treatment Annual rate: 2.30% – accidental exposure requiring adrenaline	Calculated based on the number of accidental exposures observed in the placebo group in the PALISADE trial (13 events out of 124 patients – Hourihane et al 2019), converted to annual probabilities 23% (3/13) of exposures that required treatment also required adrenaline (Hourihane et al 2019)
300, 600, 1000, 2000 mg MTD	Annual rate: 9.59% – accidental exposures requiring treatment Annual rate: 3.53% – accidental exposure requiring adrenaline	Calculated based on ARC004 results in cohorts 1 and 3A, combined and adjusted to include different durations of treatment in both cohorts (ARC004, CSR, Table 63 and Table 14.3.7.6) Rates in Cohort 1 (109 patients): 8 events of accidental exposures related to peanuts, 73% of patients with accidental exposure required treatment, 26% required adrenaline. Rates in Cohort 3A (31 patients): 8 events of accidental exposures related to peanuts, 43% of patients with accidental exposures required treatment, 14% required adrenaline.

Results of the scenario are presented in the table below. The ICER for Palforzia compared with avoidance only is £23,407 per QALY gained compared to £23,142 per QALY in the base case.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,721	26.8	20.000	21,463	0.000	0.916	23,407
Avoidance only	12,285	26.8	19.084				

B7. Section B.3.3.6. Treatment duration. The observed proportion discontinuing treatment and reasons for discontinuation during the different phases of PALISADE and ARC004 is unclear to the ERG. Please could you provide a breakdown of this and clarify the following:

a) of the [redacted] Palforzia patients in the tolerated <300mg health state at 72 weeks (B.3.3.2, page 123), the proportion that:
   i. discontinued treatment during the up-dosing or the maintenance phase of PALISADE;
   ii. were found to have MTD <300mg based on the PALISADE exit DBPCFC.

b) Please clarify also whether the model assumes immediate discontinuation of treatment for all those who have a MTD of <300mg at 72 weeks based on the PALISADE exit DBPCFC. If so, given that no food challenge is included in the model at this time point, please explain how patients/clinicians would know to stop treatment.

a) In the PALISADE trial:
   i. [redacted] patients discontinued during the initial dose escalation,
   ii. [redacted] patients discontinued during the up-dosing phase,
   iii. [redacted] patients discontinued during the maintenance
   iv. [redacted] patients did not tolerate 300mg of peanut protein in the exit double-blind placebo-controlled food challenge (DBPCFC) (PALISADE, CSR).

   In total, in the PALISADE trial, there were [redacted] patients who discontinued the Palforzia treatment or did not tolerate 300 mg of peanut protein in the exit DBPCFC.

   In the model, the estimated total number of patients who discontinued the treatment or did not tolerate 300 mg of peanut protein in the exit DBPCFC is [redacted]. It was calculated based on patient level data by applying 30 matrices with transition probabilities.

   The main reason for discontinuation before the DBPCFC were adverse events, withdrew consent, investigator decision, other.

b) The model includes immediate discontinuation of the Palforzia treatment for all patients who have a MTD of <300mg. In the clinical trials, patients had an exit DBPCFC at the end of PALISADE or ARTEMIS after approximately 1 year of treatment and also at the exit of the PALISADE follow-on study ARC004 after approximately 2 years of treatment, in order to demonstrate the efficacy of Palforzia. In real world practice it is anticipated, based on clinical opinion, that patients would optionally require only one open food challenge following successful treatment, to confirm their level of desensitisation. Aimmune believes that in clinical practice repeated food challenges would not

be deemed a good use of NHS resources and would also place an unnecessary burden on the patient and their carers. In the model therefore, one open food challenge was included at the end of the second year for all Palforzia patients who were still on treatment. However, the timing of this food challenge in real-world practice might be anywhere from around the end of year 1 to the end of year 2 (clinical expert opinion).

To show the impact of an additional food challenge in line with the clinical trials on the model results, a scenario where two food challenges are assumed for Palforzia patients has been conducted. For simplicity and due to uncertainty about the timing, the cost of two food challenges has been added to the initial dose escalation visit for Palforzia and is therefore conservatively applied to all Palforzia arm patients. The results of the scenario are presented in the table below.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,594	26.8	20.000	21,621	0.000	0.916	23,603
Avoidance only	11,973	26.8	19.084				

Utility inputs

B8. Section B.3.4.4 Health related quality of life. Given the assumption that a food challenge occurs only once in the model, at 24 months, please explain how earlier (unconfirmed) desensitisation is assumed to impact on health-related quality of life.

Please see responses for the question B7 b).

The base case scenario assumes that food challenge will take place in the last cycle in the second year (cycle 30), so at the beginning of the third year a decision about treatment continuation/discontinuation can be made.
To investigate the impact of food challenge on costs a scenario analysis that includes cost of two food challenges was conducted (see answer for the question B7 b).

Additionally, a further scenario is presented below in which no health-related quality of life impact of Palforzia treatment is assumed before the food challenge in the last cycle of the 2nd year. In this scenario all patients, in both the Palforzia and placebo arm who reach maintenance dosing, will maintain the utility achieved in the maintenance phase until the last cycle in the 2nd year regardless of MTD achieved, except patients in the <300mg MTD health state (see table below).

The utility inputs used in the scenario are presented in the table below.

Variable	Value Comment/Reference
Utility values before the food challenge (0-30 cycles)	
Up-dosing	The same as in the base case
Maintenance	The same as in the base case
<300 mg MTD	The same as in the base case
300 mg MTD 600 mg MTD 1000 mg MTD 2000 mg MTD	The same as in maintenance health state
Spontaneous tolerance	The same as in the base case
Utility values after the food challenge (from 31st cycle onwards)	
All health states	The same as in the base case

Results of the scenario are presented in the table below. The ICER for Palforzia compared with avoidance only is £23,625 per QALY gained compared to £23,142 per QALY for the base case scenario.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Palforzia	33,172	26.8	19.980	21,199	0.000	0.897	23,625
Avoidance only	11,973	26.8	19.082				

Resource use and costs

B9. Section B.3.5.5 Tables 65 and 66. Costs of anaphylactic reactions and accidental exposures requiring adrenaline. Please provide further rationale for the assumption that all accidental exposures requiring adrenaline incur ambulance attendance and A&E costs, whereas only a proportion of mild and moderate

treatment related anaphylactic reactions requiring adrenaline incur ambulance attendance and A&E costs.

An accidental exposure reaction/ systemic reaction requiring adrenaline is an unpredictable and highly stressful emergency situation which occurs unexpectedly, often when the child is at school or away from home and their parents or carers. Clinical advice in such instances is to use an adrenaline pen and call an ambulance. In contrast, mild and moderate anaphylactic reactions due to treatment are more predictable and usually occur in proximity to the dosing of Palforzia and usually at home when the carer will be supervising the child as per the Palforzia prescribing guidelines. Carers become more familiar with the signs of reactions and when and how to respond and seek medical help, hence the use of ambulance and A&E resources would be expected to be lower compared to accidental exposures causing a systemic reaction.

These assumptions were discussed and validated with a UK clinical expert (Company submission, section 3.5.5 and 3.5.6).

B10. Section 3.5.1, Table 62. Initial escalation visit. Please provide further details and justification for the resource use assumptions at the initial dose escalation visit (i.e. what is done, who does it, and in what setting (outpatient / day-case) is it conducted)

Initial dose escalation (IDE) is administered on a single day under the supervision of a healthcare professional in a healthcare setting with the ability to manage potentially severe allergic reactions, including anaphylaxis (Palforzia SmPC). The IDE resources assumed in the model are deliberately conservative compared to the SmPC minimal requirements, and were reviewed with a clinical expert who considered that the IDE visit would likely be considered as a day case. The following administration schedule was assumed for IDE of Palforzia:

- Education: Education about Palforzia administration, efficacy and safety that would take 30 minutes and would be provided by an allergist.

- Administration: At this phase increasing doses of Palforzia in sequential order from 0.5 mg to 6 mg are administered, each separated by an observation period of 30 minutes.
    - Before starting the IDE schedule, the allergist carries out tests to confirm the patient is well and able to receive treatment (e.g. asthma symptoms, PEFR/spirometry, checking the patient is not sick.)
    - Before each dose is given, nurse time is needed to open the capsules and mix appropriately with food. Also, the nurse needs to give the mix to the patient for each dose level.
    - Before the next dose is given, after the observation period, a few minutes of physician or nurse examination is needed, and the patient is asked to describe any symptoms.
    - After the final dose of IDE has been given and tolerated, and before the patient leaves the clinic, guidance is provided on what to do if the patient has a reaction at home, and how to start taking the 3 mg kit at home (including education around co-factors, how to use adrenalin, most frequent adverse events, etc). These activities can be performed while observing the patient after the last dose.
    - It was assumed that the above administration of Palforzia would require 1 hour of allergist time and 3.5 hours of nurse time.
- Monitoring: alongside and subsequent to administration of Palforzia, monitoring is recommended by an additional nurse, up to at least 1 hour after final dose of Palforzia. In the model it was conservatively assumed that this would require 4 hours of a nurse's time although efficiencies could be achieved if several patients were offered IDE at once, with a nurse deemed able to monitor up to 4 patients concurrently.

Section C: Textual clarification and additional points

References and studies citations

C1. Document B, Section B.2.2 Citation numbers are missing from this section. Please clarify the corresponding references in the reference pack for ARC002, ARC007, ARC008 and ARC0011.

The following documents are provided alongside this response:

- CSRs for RAMSES (ARC007) and ARC011 are provided as AiC alongside this response.
- Publication for ARC001 (Bird JA et al. Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial. *J Allergy Clin Immunol Pract.* 2018;6(2):476-485 e473)
- Abstract and presentation for ARC002 (Bird JA et al. Oral desensitization to peanut using AR101 peanut oral immunotherapy in a roll-over safety study ARC002. Presented at the American College of Allergy, Asthma & Immunology 2018 Annual Scientific Meeting; 19 Nov. 2018)
- Poster for ARC008 (Casale et al. Safety of Peanut (*Arachis Hypogaea*) Allergen Powder-dnfp in Children and Teenagers With Peanut Allergy: Pooled Analysis From Controlled and Open-Label Phase 3 Trials Over 3.5 Years. Poster presented at the American Academy of Allergy, Asthma & Immunology 2021 Annual Meeting; February 26-March 1 2021) – This study is ongoing, and interim results are only available in the pooled safety study.

Revised text for Section B.2.2 with citations:

In total, two relevant RCTs were identified: two Phase 3 trials reporting evidence for Palforzia: PALISADE (ARC003) and ARTEMIS (ARC010).[4,5] In addition, the search also identified an open-label follow-on study to the PALISADE study (ARC004).[6] Another two Phase 3 trials (RAMSES [ARC007][7] as well as its respective open label

extension study ARC011[8]) were excluded since they only assessed safety and tolerability, not efficacy, and were conducted only in the United States (see Section 2.10.1 for information on pooled safety analysis). Two Phase 2 studies were also identified (ARC001[1] and its open-label extension study ARC002[2,3]); these were not included in the cost-effectiveness model nor the SmPC since both trials were Phase 2, relatively small in number (N=55 in ARC001 and N=47 in ARC002) and conducted only in the United States. The results of both studies were consistent with those obtained in the Phase 3 trials and do not add greater insight regarding the efficacy of Palforzia in a meaningful way. They are therefore not discussed further.

Finally, ARC008 is an ongoing open-label extension study for patients continuing on Palforzia treatment after rolling over from ARC002, ARC004, ARC010, ARC007 and ARC011. The objective of ARC008 is to provide ongoing safety monitoring and continuity of Palforzia treatment pending commercial availability. As an ongoing, unpublished safety-only study, interim results are discussed briefly in the safety section B.2.10 only.[9]

1. Bird JA, Spergel JM, Jones SM, et al. Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial. *J Allergy Clin Immunol Pract.* 2018;6(2):476-485 e473.
2. Bird JA, Welch M, Spergel J, et al. Oral desensitization to peanut using AR101 peanut oral immunotherapy in a roll-over safety study ARC002. American College of Allergy, Asthma & Immunology 2018 Annual Scientific Meeting; 19 Nov. 2018, 2018; Seattle, WA.
3. Bird JA, Welch M, Spergel J, et al. Oral desensitization to peanut using AR101 peanut oral immunotherapy in a roll-over safety study ARC002. *Ann Allergy Asthma Immunol.* 2018;121.
4. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med.* 2018;379(21):1991-2001.
5. Hourihane JO, Beyer K, Abbas A, et al. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Child Adolesc Health.* 2020;4(10):728-739.
6. Vickery BP, Vereda A, Nilsson C, et al. Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study. *J Allergy Clin Immunol Pract.* 2020.
7. Aimmune Therapeutics. Clinical Study Report. Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES). 2018.

8. Aimmune Therapeutics. Clinical Study Report. Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children, Active Treatment Arm Open-Label Extension Study (RAMSES OLE). 2020.
9. Casale TB, Burks AW, Baker J, et al. Safety of Peanut (*Arachis Hypogaea*) Allergen Powder-dnfp in Children and Teenagers With Peanut Allergy: Pooled Analysis From Controlled and Open-Label Phase 3 Trials Over 3.5 Years. Poster presented at the American Academy of Allergy, Asthma & Immunology 2021 Annual Meeting; 2021 February 26-March 1. 2021.

NICE National Institute for Health and Care Excellence

Patient organisation submission

AR101 for treating peanut allergy [ID1282]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Allergy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Allergy UK is the leading national patient charity for people living with all allergies and provides support, advice and information for individuals living with allergic disease. Allergy UK aims to raise the profile of allergy at all levels, with a vision for everyone affected by allergy to receive the best possible care and support, working together with government, professional bodies, Healthcare Professionals and corporates towards our vision, to help improve the lives of the millions of people with allergic disease. Allergy UK is a registered charity and receives funding through public donations and through the British Allergy Foundation a not for profit company. During 2019-20 Allergy UK reached out to 82,000 via the website, over 2.5 million via social media platforms and advised over 9,000 individuals with allergies via the helpline and email contacts
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Allergy UK has not received any funding from Aimmune in the last 12 months. We are in discussions to secure funding for 21/22 of £11,146 for sponsorship of an Allergy UK webinar and sponsorship of an article in Allergy Today. Products are not advertised and information is on Disease education.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No Allergy UK does not work with the tobacco industry or have any links with the tobacco industry
5. How did you gather information about the experiences of patients and carers to include in your submission?	Allergy UK engages with families, young people and adults to gather information in order to most effectively support the allergic community and their needs. We do this through surveys and research, and calls to our Helpline provide us with valuable insights into the kind of resources that will be most helpful for people living with allergic conditions, including food allergies. Allergy UK also runs a dedicated dietetic clinic resource that callers to the helpline can access if they are not currently receiving any dietetic support for their child. Anonymised data from this resource as well as collaboration on a number of projects to explore the impact of living with food allergies has helped to build up a profile of patient needs relating to food allergy The Allergy UK website has an area devoted to food allergies, with information and Factsheets for people living with food allergies, with testimonies and case studies from individuals living with the condition, highlighting the impacts it has on their daily lives. Our database is segmented in a way that allows us to be able to communicate with people living with food allergies for our fact-finding initiatives and for the dissemination of information and support. We are currently working on a range of projects targeting both sufferers and Healthcare professionals with a range of new educational resources.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	At present there is no cure for food allergy, with treatment and management involving complete avoidance of the trigger foods and the ability to recognise and treat allergic reactions if there is accidental exposure to the trigger foods – for example, through ingestion or cutaneous exposure. Food allergy currently affects approximately 6% of children and 2-3% of teenagers, with manifestations ranging from mild symptoms to life-threatening anaphylaxis. Food allergy can cause anxiety and fear in individuals of all ages and the psychosocial impact of food allergy is huge, affecting social activities such as eating out, any social activity, schooling and work environment, relationships, career choice and confidence. 'My daughter is 7 and she has had a peanut allergy. She recently has had an epi pen and she now is refusing to eat more and more foods because she is scared of having to use the epi pen and go to hospital.' 'My son who is 13 has a peanut and hazelnut allergy. He is now of an age where he is going out without me. It really panics me about who would administer the epipen' 'My daughter who lives with her mother was diagnosed 3 years ago with a peanut allergy. She has an epipen but my daughter will not stay with me as she says she doesn't feel safe.' 'I have an anaphylactic allergy to Peanuts, which I have had since the age of three. I had no severe reactions until early this year when I went into anaphylactic shock after eating no more than half a teaspoon of food containing the allergen. As a result of this incident, I was hospitalised, and have also been made permanently unfit for my dream career of life at sea. ' Food allergies cause a lot of anxiety and concern and there is a general lack of skills and knowledge surrounding food allergy especially round adults with food allergies and reintroduction of foods for their infant children. 'I am starting to wean my 6 month old daughter this week however I have a severe allergy to peanuts and nuts, causing anaphylaxis and requires epipens. Please can you advise when i should introduce these

	food allergens to my baby and in what amounts/for how long? Or will she need to be allergy tested before introducing them? I am particularly worried about peanuts, as my allergy has greatly impacted my life and i want to prevent the same happening to her.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments available on the NHS are designed to treat the symptoms of an allergic reaction if the food is ingested, this means that individuals and their families with severe peanut allergy live constantly with the anxiety and fear that they may accidently ingest peanut and this can lead to severe life threatening allergic reactions, this has a huge impact on quality of life and psychosocial wellbeing.
8. Is there an unmet need for patients with this condition?	Yes, to have a treatment available that can help build a tolerance – even to small amounts of peanut and reduce the possibility of a severe allergic reaction if there are trace amounts accidently ingested in foods will have a huge impact on quality of life. For instance this will make reading food labels (may contain, make in a factory that contains) and eating out so much easier.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	A lot of patients and their families are keen to try the new therapy as they feel that this may a way forward to managing their child's peanut allergy 'I have a severe peanut allergy and I was wondering if there are literally any treatments to lessen the severity of the allergy. Even if my allergy was slightly less serious, I could do so many more things.' We have lots if enquires through the helpline to ask about offering themselves for clinical trials or details of private clinics offering immunotherapy to peanuts – it would be advantageous for this therapy to be

	available on the NHS so that the therapy can be regulated and monitored - patients usual medical professional can monitor and be aware of side effects and when prescribing other medications etc 'I'm allergic to nuts, in particular peanuts. I'm also asthmatic and anaphylactic. I'm interested in microdosing to build up tolerance. Can you point me in the direction of any studies or healthcare providers who will help provide this in a controlled environment?'
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The only disadvantages raised have been risk of reaction to peanut therapy and that the therapy may not be available widely across the NHS but be restricted to more wealthy geographical areas
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Special consideration must be given to teens and young people who have food allergy, this is due to fact this age group has been shown to be most at risk of mortality from severe life threatening allergic reactions to food and also to prevent or reduce the impact especially psychologically at a crucial time when young people are exploring their independence, it is recognised that that the psychosocial impact of having food allergies is greater than having diabetes and can evolve with severe manifestations of this condition and last into their adult years.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	At present allergy services are not equally distributed across the UK and so access to this treatment may be dependent on your geographical rea and access to specialist allergy services. It is important to take into account access to treatment needs to be implemented fairly across all socio demographics with thought to reduce healthcare inequalities such as post code lottery for referral or individuals having to travel to a different part of the U.K. for access to treatment etc.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. What are the psychological effects of living with a peanut allergy? How does this affect your day-to-day quality of life?	The effect of food allergy on mental health is enormous, having a food allergy can cause great anxiety and fear, not only for the individual affected but also for their families and friends. Has an impact on eating socially – with need to always feel prepared to bring a safe snack just in case what is on offer is not suitable. Need to always bring rescue medication just in case of an allergic reaction, and prepping family and friends what to do in an emergency. Needing to be confident and assertive to ask waiting staff / food prep about allergens in food. Reading and interpreting food labels for everything you consume, not being able to let your guard down and have a day off – you feel always on 'high alert ' in case your allergen is in the food accidentally. It can also be very frustrating and can feel mentally wearing to have a food allergy , you feel different to your peers and this can lead to social embarrassment – having to ask what is in foods can lead people to view you as fussy .

	Some people with food allergies can develop food eating disorders, social anxiety and depression caused by their food allergy . There have been instance of school and work place bullying due to food allergies.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Food allergy has a huge impact on an individual and families quality of life
- Food allergy also has an enormous mental health effect
- Teens and young people are at greater risk of dying from severe food allergic reactions
- Current treatment options only manage an acute allergic reaction and do not address the root cause
- Immunotherapy for peanut could have potentially life changing impact on individual and their families with peanut allergy

Thank you for your time.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Anaphylaxis Campaign
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Anaphylaxis Campaign is the only UK wide charity focused on supporting those at risk of severe allergies. We have been providing information and support to patients and their families for over 27 years. We have approx. 3000 individual members, 260 healthcare professional members and 120 corporate members. We receive no government funding or grants and rely on a broad base of different sources of funding including donations and partnership working with companies, individuals, stakeholders and third-party organisations.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Aimmune – 15/10/20 - £2248 for review of survey, interview guide and other research materials Aimmune –15/10/20 - £936 Expert review of AR101 educational materials Aimmune 26/05/20 - £155 – Corporate membership fees.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient feedback via our helpline service, support groups and members. Our members include individuals and families living with severe allergies and at risk of anaphylaxis as well as healthcare professionals working within the speciality of allergy.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with or caring for someone with severe allergies has implications for many different areas of daily living including :- **Shopping and Preparing Food –** • extra time reading labels • extra cost for free-from foods • recipes can change so need to check labels with every purchase • understanding the meaning of 'may contain' labels on packaging • avoiding cross contamination in the kitchen

- extra time cooking from scratch
- weaning an infant with allergies – how and when?

Eating Out –

- Some foods seen as too high risk e.g. Asian food & nuts
- extra communication needed with restaurant
- lack of awareness in staff of allergy issues
- lack of options on menu – reduced choice
- risk of cross contamination
- buffets problematic – high risk of cross-contamination
- difficult socially or at work with catered events and shared kitchens– social exclusion
- having to carry adrenaline everywhere – must carry medication at all times

Travelling –

- Flying can be stressful – enclosed air space - difficult to avoid allergen
- Airline may not be accommodating e.g. serving allergen to other travellers in confined spaces
- have to have GP letter to carry adrenaline on plane
- difficulties communicating allergy in foreign language
- hard to get adequate travel insurance
- may have to pack ‘safe’ foods for emergencies

Seasonal Events –

- often heavily based around foods e.g. chocolate at Easter, nuts at Christmas
- Family members may lack understanding and prepare unsafe food or gifts
- Pressure to consume religious or cultural foods that are unsafe

	Young People - • Young people between 16-24 years old are frequently recognised as being most at risk of anaphylaxis. • Decrease in parental support – leaving home for the first-time managing allergy independently • More risk taking – experimenting with new foods, travelling alone, alcohol potentially affecting decisions • Reluctance to carry adrenaline auto-injectors and to tell peers about their allergies **Education – Parents have to consider -** • Choosing a school for a child with severe allergy – is the school 'Allergy aware'? • Putting in place an individual healthcare plan for the child • Does the school hold 'spare' adrenaline auto-injectors in line with government guidance? • Have the staff had allergy and anaphylaxis first aid training? • Will the child have access at all times to their own two adrenaline auto-injectors? • Does the school undertake an annual allergy risk assessment? • Does the school have policies for children with medical conditions including allergies? • Are the catering facilities allergy aware and inclusive?

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The only current way to manage severe allergy is complete avoidance of the allergen and carrying two adrenaline auto-injectors as emergency treatment in case of accidental exposure. **Patients/Carers report -** • Lack of understanding in primary care - appropriate referral, treatment, support and education • Can be a long wait to see a specialist and get a diagnosis or follow-up • uncertainty about when to use medication • confusion about how many adrenaline auto injectors to carry • understanding how and when to use adrenaline auto injectors • concerns about setting up a care plan – care and safety at school • lack of appropriate NHS followup following emergency treatment for anaphylaxis (in line with NICE CG134)
8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need. There are currently no effective treatments available on the NHS to reduce the severity of an allergic reaction from accidental peanut exposure. The development of AR101 is widely and eagerly anticipated by families with children who may be eligible for the treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients/Carers report that they believe this treatment will - • reduce the burden of managing all of the implications of living with a severe allergy outlined in section 6 above due to decreased risk of a severe allergic reaction. • Reduce the psychological burden of living with anaphylaxis as outlined in section 14 below.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients/carers report concerns about - • Burden of maintaining the schedule of daily treatment • Risk of side effects – potential for mild, moderate or severe allergic reactions • Burden of monitoring child for side effects • Psychological effect on child if side effects experienced • Psychological issues around consuming allergen previously strictly avoided. • Concerns about longevity of results following conclusion of treatment
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	With young people between 16-24 years old recognised as being most at risk of anaphylaxis, there may be an argument for prioritising treatment for the older end of the suggested treatment range of 4-17 years in order to offer the most protection to those most at risk.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	All eligible families should have equal opportunity to access the technology with patient information available in a variety of accessible formats to cater for a diverse range of needs.
Other issues	
13. Are there any other issues that you would like the committee to consider?	• Consider that treatment will likely reduce the number of severe allergic reactions as a result of accidental exposure, thus reducing need for hospital admissions and costly emergency care.
14. What are the psychological effects of living with a peanut allergy? How does this affect your day-to-day quality of life?	Living at risk of anaphylaxis can cause extreme anxiety – especially if the cause is unknown or it is a difficult allergen to avoid. Experiencing anaphylaxis is often very traumatic and individuals can become so anxious they find it hard to tell the difference between a severe allergic reaction and a panic attack. Quality of Life - • **Infant –** issues around weaning – what and when, childcare issues – ensuring safety and awareness with third party caregivers and relatives such as grandparents/parental anxiety and trauma- anaphylaxis is a life threating condition • **School Age child –** Ensuring safety at school - Allergy Action plans/spare pens in schools/staff training and awareness/risk assessment/bullying due to allergy/parental anxiety/ having to 'let go'

	• **Adolescent –** Increased risk-taking behaviour/denial – not wanting to be different/embarrassed to ask questions eating out/ reluctance to carry AAIs/parental issues with letting go – transfer of responsibility for managing the allergy • **Adults –** May be issues at work securing reasonable adjustments (severe allergy CAN be considered a disability for the purpose of the Equality Act though little actual precedence) Young adults still at increased risk of severe reaction for reasons outlined under adolescence/ can be more difficult to access adult allergy services – often not reviewed for many years/

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- This is a much needed and long-awaited technology
- Living with peanut allergy has a major impact on all aspects of daily life
- Treatment will alleviate the significant financial burden of living with severe peanut allergy
- Treatment is expected to significantly reduce the psychological burden of living with severe peanut allergy
- Potential reduction in allergic reactions will reduce NHS burden of treatment including emergency care

Thank you for your time.

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Palforzia for treating peanut allergy [ID1282]

Produced by **Aberdeen HTA Group**

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Date completed 30 July 2021

Contains [redacted]/[redacted]

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number **134167**.

Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

The authors are grateful to Bev Smith for her clerical assistance.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be cited as follows: Cruickshank M, Boyers D, Scott N, Robertson C, Manson P, Lumsden C, Scotland G, Brazzelli M. Palforzia for treating peanut allergy [ID1282]. Aberdeen HTA Group, 2021.

Contribution of authors

Moira Cruickshank and Clare Robertson critiqued the clinical effectiveness evidence submitted by the company; Neil Scott checked and critiqued the statistical analyses presented in the company submission; Graham Scotland led the cost-effectiveness side of the appraisal and together with Dwayne Boyers reviewed and critiqued the cost-effectiveness evidence and undertook further exploratory and sensitivity analyses; Paul Manson checked and critiqued the company's search strategies; Colin Lumsden provided clinical guidance throughout the appraisal and comments on this report. Miriam Brazzelli led the clinical effectiveness side of the appraisal and coordinated all its aspects. All authors contributing to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
A&E	Accident and emergency
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DBPCFC	Double-blind placebo-controlled food challenge
EMA	European Medicines Agency
ERG	Evidence review group
EPAR	European public assessment report
EQ-5D	EuroQol-five dimension
EQ-5D-Y	EuroQol-five dimension (youth)
FAIM	Food allergy independent measure
FAQLQ	Food-allergy-related quality of life questionnaire
FDA	US Food and Drug Administration
GI	Gastrointestinal
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICER-US	Institute for clinical and economic review – United States
IDE	Initial dose escalation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IPD	Individual participant data
ITT	Intention to treat
LY	Life year
MED	Minimal eliciting dose
MID	Minimally important difference

MTD	Maximum tolerated dose
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OIT	Oral immunotherapy
OWSA	One-way sensitivity analysis
PA	Peanut allergy
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Q	Quartile
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SG	Standard gamble
SHELF	Sheffield elicitation framework
SmPC	Summary of product characteristics
SoC	Standard of care
TEAEs	Treatment-emergent adverse events
TRAEs	Treatment-related adverse events
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
TTO	Time-trade-off

1. Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The focus of the submission received from Aimmune Therapeutics is Palforzia for treating peanut allergy in children aged 4 to 17 years.

The clinical evidence is provided mainly by data from a Phase 3 international, double-blind, placebo controlled RCT, PALISADE (ARC003) and its follow-on study, ARC004, with data from a further RCT, ARTEMIS (ARC010), used in sensitivity analyses. A Phase 2 RCT that was identified in the company's literature review (ARC001) was not included in the CS as it included only 55 participants and was conducted solely in the USA. The ERG considers that ARC001 was eligible for inclusion but that its findings were in line with the CS and would not materially change the company's conclusions. The clinical outcomes used in the economic model are peanut allergy desensitisation, systemic allergic reactions (including anaphylaxis), frequency and severity of symptoms after accidental exposure to peanut, treatment discontinuation up to the end of follow-up, and adverse effects of treatment.

The primary efficacy endpoint of peanut allergy desensitisation (defined as the proportion of participants who tolerated a single highest dose of at least 1000mg of peanut protein [2043mg cumulative] without dose-limiting symptoms) was met in

both PALISADE and ARTEMIS. Accidental exposure to peanut was low across both trials, with few participants requiring subsequent adrenaline use and any associated symptoms generally being moderate at worst. Discontinuations in an integrated safety population (n=944) were reported in the CS as 11.4%, with three participants discontinuing due to anaphylaxis. Health-related quality of life did not change between baseline and study exit of PALISADE and ARTEMIS. The patterns of adverse events were as expected in this patient population.

The company did not conduct a meta-analysis due to differences in study design across the identified trials.

The company developed a decision analysis model to estimate the cost-effectiveness of Palforzia + avoidance compared to avoidance only. Where possible, the model was populated with data from the PALISADE study and the ARC004 extension study. Data sourced from the ARTEMIS study were considered as sensitivity analysis. Patient health state utility values and carer disutility were obtained from a *de novo* utility study and risk of accidental peanut exposure was obtained from a risk quantification study. Long term treatment discontinuation was informed using clinical expert elicitation.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1 Summary of key issues

Issue	Summary of issue	Report sections
1	Timing of food challenges including the timing at which utility gains are realised in clinical practice	4.2.2, 4.2.7, 4.2.8
2	Long term assumptions about treatment discontinuation and transition from peanuts in diet to avoidance	4.2.2 4.2.8
3	Patient health state utility values	4.2.7
4	Resource use associated with anaphylactic reactions and adverse events.	4.2.8

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are

- The company prefers to assume that the quality-of-life benefits of improved peanut tolerance can be realised prior to a food challenge being conducted. The ERG considers that in clinical practice, Palforzia treated patients would receive one food challenge, avoidance patients would receive none, and utility benefits of improved tolerance could only be achieved after the food challenge results are available to patients, their parents / guardians, and their clinicians.

- The company prefers patient quality of life obtained from a mix of adolescent reported (N=40) and carer proxy (N=117) reported data. The ERG prefers the use of adolescent self-reported data only because patients with experience of the condition are the best judge of its impact on their quality of life and it may be possible that carer proxy valuations include the impact of carer anxiety and worry, which is already captured separately in the model.

- The company prefer inclusion of the most common adverse events and anaphylactic reactions, whereas the ERG prefers inclusion of all events that could impact on costs or benefits, even if rare. The company assume that the costs of treating a treatment related anaphylactic reaction are lower than a patient with accidental peanut exposure. The ERG prefers to assume that all

patients who require adrenaline would also need an ambulance and transport to hospital, regardless of whether the event was caused by treatment or by accidental exposure.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, Palforzia is modelled to affect QALYs by:

- Improving tolerance to peanut and allowing a substantial proportion of people to include peanuts in their diet for the rest of their lives
- Reducing the number of people who will remain with a low peanut tolerance of <300mg
- Reducing the risk of accidental exposure to peanut
- Improving quality of life for both patients and their carers (carer benefits included until the patient reaches age 18)

Overall, the technology is modelled to affect costs by:

- Introducing a new treatment which increases the costs of treating peanut allergy

The modelling assumptions that have the greatest effect on the ICER are:

- The true proportion of patients that will discontinue Palforzia treatment and include peanuts in their diet longer term (i.e the proportion of the modelled cohort who achieve long-term treatment benefit after treatment discontinuation)
- The true difference in health-related quality of life for patients who cannot tolerate 300mg, compared to patients who can tolerate 2000mg (approx. 6-8 peanuts) or can include peanuts in diet.

1.3 The decision problem: summary of the ERG's key issues

In general, the company decision problem is in line with the NICE final scope and no major issues were identified by the ERG. The CS addresses a more specific population than that specified in the NICE final scope and focuses on patients aged 4 to 17 with a confirmed diagnosis of peanut allergy who are under the care of a specialist physician, including patients who turn 18 years old during therapy (see Section 2.3 for further details). The ERG in consultation with their clinical expert considers the company's description of the current treatment pathway and treatment options available for young people suffering from peanut allergy accurate and agrees with the company's positioning of Palforzia in the treatment pathway.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The company did not conduct any meta-analyses and chose to focus on patient-level data from PALISADE with data from ARTEMIS used in sensitivity analyses. The ERG is of the opinion that the reasons for excluding the ARC001 study were not justified, and an acceptable approach would have been to pool data from all three randomised studies to limit the chance of selection bias. However, the ERG recognises that there are important differences in study design across studies and, that all studies yielded similar results. Therefore, results based on aggregated data would not have made a major difference to the conclusions.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The company's base case ICER is £21,581 per QALY gained and remained unchanged following response to clarification queries. There are four key areas of uncertainty that drive differences in the company and ERG preferred base cases. These are summarised below.

Issue 1 Timing of food challenges including the timing at which utility gains are realised in clinical practice

Report section	Sections 4.2.2, 4.2.7 & 4.2.8
Description of issue and why the ERG has identified it as important	The timing of treatment discontinuation and realisation of utility benefits are based on food challenges (2 for Palforzia, 1 for avoidance) conducted as part of the clinical trials, but food challenges are likely to be less common in routine clinical practice. This is important because the cost savings of treatment discontinuation (for reasons other than TRAEs or accidental exposure) and realisation of utility gains can only be achieved once a patient, their parents / guardians and clinician become aware of the maximum tolerated dose as part of a food challenge.
What alternative approach has the ERG suggested?	Based on clinical expert opinion and the company's response to clarification, the ERG prefers the use of one food challenge (at about 2 years) for Palforzia and none for avoidance. Treatment costs are applied up until the food challenge (for all except those with a TRAE or accidental exposure) and utility benefits of known MTD are realised only after the food challenge has been completed. Similarly, in the avoidance arm, utilities for MTD 300mg, 600mg and 1000mg are assumed to never be realised as no food challenge would be conducted.
What is the expected effect on the cost-effectiveness estimates?	Adding Palforzia treatment costs, and delaying utility gains increases the ICER for Palforzia, whereas assigning the same utility ("MTD: <300mg") to all tolerance states in the avoidance arm reduces the ICER. The net impact is a small increase in the company's base case ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that further validation from multiple clinical experts regarding both the number and timing of food challenges for patients treated with Palforzia and avoidance only in clinical practice would help reduce uncertainty.

Issue 2 Long term assumptions about treatment discontinuation and transition from peanuts in diet to avoidance

Report section	4.2.6
Description of issue and why the ERG has identified it as important	Transition probabilities to inclusion of “peanut in diet” and from “peanut in diet” to avoidance are based on clinical expert opinion (elicited using SHELF) but are highly uncertain. The validity of the following assumptions may be questionable: 1) Transition to peanuts in diet relies on the opinion of [redacted] clinical expert, rather than all included in the SHELF. 2) The validity and derivation of [redacted] is unclear. These parameters drive cost-effectiveness results because they determine the proportion of Palforzia treated patients who can achieve a lifetime of treatment benefit without incurring long-term treatment acquisition costs.
What alternative approach has the ERG suggested?	The ERG conducts further scenario analyses to explore the uncertainty in these key assumptions.

What is the expected effect on the cost-effectiveness estimates?	Scenarios that reduce the probability of transitioning to “peanut in diet” increase the ICER substantially, whereas scenarios that increase the probability of transitioning from peanut in diet back to avoidance also increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Further consultation (data) on clinical experience of managing the transition on Palforzia treated patients to regular inclusion of peanut in diet would help validate the parameter estimates used in the model. The company should specifically justify A) the source and appropriateness of the assumption [redacted] and B) the assumption that [redacted].

Issue 3 Patient health state utility values

Report section	4.2.7
Description of issue and why the ERG has identified it as important	The company prefers the use of patient HSUVs, collected in a utility study, based on EQ-5D-Y responses to health states described to mirror model states. Data were obtained from a mix of N=40 adolescents with experience of peanut allergy ([redacted]) and N=117 parent / guardian (of children with peanut allergy) proxy provided responses. The ERG prefers patient reported responses only. This issue is an important driver of cost-effectiveness because the difference between tolerating 2000mg (6-8 peanuts) and tolerating <300mg is much higher when carer proxy valuations are included than when the sub-sample of adolescents with experience of peanut allergy is used to derive HSUVs
What alternative approach has the ERG suggested?	The ERG prefers the use of the sub-sample of adolescents with experience of peanut allergy because 1) it is more appropriate to use EQ-5D-Y responses elicited from patients wherever possible and 2) there is a risk that carer proxy valuations include some concern and anxiety of carers as well, which would mean double counting of carer disutilities already incorporated in the model.
What is the expected effect on the cost-effectiveness estimates?	Applying the ERG's preferred data would reduce the QALY gains for Palforzia and thus substantially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that all the required evidence is available from the company's utility study.

Issue 4 Resource use associated with anaphylactic reactions and adverse events.

Report section	4.2.8.
Description of issue and why the ERG has identified it as important	The company assume that the resource use requirements for treating an anaphylactic reaction to Palforzia are lower than a patient who has an anaphylactic reaction due to accidental peanut exposure. This is an important issue because it reduces the costs of managing treatment related adverse events relative to accidental exposure and may generate a moderate bias in the ICER in favour of Palforzia.
What alternative approach has the ERG suggested?	Based on the ERG's clinical expert opinion, the ERG prefers to assume that all patients who require adrenaline due to an anaphylactic reaction would incur the same resource use (i.e., they would need an ambulance and transport to hospital), regardless of whether the event was caused by treatment or by accidental exposure.
What is the expected effect on the cost-effectiveness estimates?	Applying the ERG's preferred assumption leads to a moderate increase in the ICER for Palforzia.
What additional evidence or analyses might help to resolve this key issue?	Further real-world data, or clinical expert opinion from a range of clinical experts would be helpful in determining the validity of the company's assumptions.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred base case ICER incorporates the cumulative impact of the following assumptions:

- The ERG prefers assumptions where the HSUVs associated with a change in tolerance level are realised only after the results of a food challenge become known. The ERG's clinical expert opinion is that, in routine clinical practice, Palforzia treated patients would receive one follow-up food challenge at about 2 years, whereas avoidance patients would receive none (Scenarios 1, 4 and 5).

- The ERG also prefers an assumption that Palforzia will continue treatment until the results of a food challenge become known unless they have a TRAE or accidental exposure (Scenario 2).

- The ERG prefers HSUVs sourced directly from the adolescent (N=38) sub-sample of the company's *de novo* utility study who have experience of peanut allergy, as opposed to the company base case which combines adolescent self-reported and carer proxy (N=157). The ERG also considers direct valuation to minimize any risk of carer proxy double counting of their own disutility, which is included separately in the model (Scenario 3).

- The ERG prefers the inclusion of severe anaphylactic reactions and all moderate and severe TRAEs, even if event occurrences are rare (scenarios 8 and 9).

- The ERG prefers resource use for anaphylactic reactions that require adrenaline set equal the resource use associated with accidental exposures that require adrenalines. This applies an assumption across TRAEs and accidental exposures, whereby all patients that require adrenaline will also require an ambulance and a visit to A&E (Scenario 10).

- Finally, the ERG prefers the use of ambulance transfer unit costs sourced from NHS reference costs (Scenario 11).

The individual impact of each of the ERG's preferred assumptions on the ICER is detailed in Table 2. The final two rows of the table show the cumulative impact of all

the ERGs preferred assumptions on the deterministic ICER (£36,565 per QALY gained) and probabilistic ICERs (£39,716 per QALY gained) respectively.

Table 2 Summary of ERG's preferred assumptions and the ICER

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company base-case	5.1	19,769	0.916	21,581
+ Apply maintenance utility up to the timing of the food challenge	4.2.2 4.2.7	19,769	0.897	22,031
+ Apply Palforzia treatment costs (i.e., remove discontinuation assumption) from end of up-dosing to timing of the food challenge	4.2.2 4.2.8	19,829	0.897	22,097
+ HSUVs based on self-reported data (adolescent sample, N=38)	4.2.7	19,829	0.577	34,376
+ Remove up-dosing and maintenance utilities from avoidance arm (set equal to "MTD: <300mg" state)	4.2.2 4.2.7	19,829	0.541	36,641
+ Set all HSUVs and carer disutility equal to current health state (i.e., MTD: "<300mg") in the avoidance arm	4.2.7	19,829	0.560	35,393
+ Include severe anaphylactic reactions	4.2.8	19,975	0.560	35,660

+ Include all moderate and severe TRAEs	4.2.8	20,056	0.559	35,847
+ Set treatment related anaphylactic reaction = accidental exposure resource use	4.2.8	21,063	0.559	37,647
+ Apply NHS reference costs for ambulance usage	4.2.8	20,458	0.559	36,565
ERG preferred deterministic ICER (Combination of all scenarios above)	**6.3**	**20,458**	**0.559**	**36,565**
ERG preferred probabilistic ICER (Combination of all scenarios above)	**6.3**	**22,738**	**0.573**	**39,716**

Further details of additional scenario analyses conducted by the ERG, together with justifications for these analyses are provided in Section 6.2 and 6.3. Section 6.3 also includes the results of applying company conducted scenario analyses to the ERG's preferred base case set of assumptions.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The submission received from Aimmune Therapeutics focuses on the treatment of peanut allergy in children aged 4 to 17 years who are under the care of a specialist physician, including patients who turn 18 years old during therapy. The company's description of the prevalence, symptoms and complications of peanut allergy is generally accurate and in line with the decision problem. The relevant intervention for this submission is Palforzia (AR101).

2.2 Background

Please refer to the background section for the ERG's critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention.

Food allergy is defined as an immune-mediated hypersensitivity reaction to the ingestion, inhalation or skin contact of food and may be divided into Immunoglobulin E (IgE) mediated (immediate-onset) and non-IgE mediated (delayed-onset) reactions.[1] Peanut allergy is one of the most common food allergies, affecting between 0.5% and 2% of children in the UK.[2] The prevalence of childhood peanut allergy has increased in recent decades, with the numbers of affected children aged under 18 years of age increasing 5-fold in the years 2000 to 2015, from 116 per 100,000 children to 635 per 100,000 children in the UK, although prevalence estimates may be problematic due to variances in diagnostic criteria and methods.[3, 4] A formal diagnosis of peanut allergy usually results from referral to secondary or specialist care following an initial presentation to a GP or hospital accident and emergency department following an allergic reaction caused by peanut exposure.[5] Investigation for suspected IgE mediated immediate/acute reactions include skin prick and serum specific IgE testing. Annual healthcare costs associated with peanut allergy have been reported to be between £33 to 44 million, reflecting an increased need for primary and secondary care contacts, hospital admissions and prescription medications.[3]

The median estimated amount of peanut triggering an allergic reaction is 125 mg of peanut protein (approximately half a peanut kernel), although even trace amounts of less than 5 mg of protein can cause allergic reactions in individuals, making it very difficult to avoid all exposure to peanuts in everyday life.[6-8] The frequency and severity of allergic reactions are highly unpredictable and the severity of symptoms in an individual may not be consistent with the severity of future reactions. It is, therefore, not possible to predict the likelihood or severity of an individual's allergic reaction, even with detailed knowledge about a patient's previous reactions.[5] Common symptoms in response to an allergic reaction include rash, vomiting, abdominal pain, wheezing and throat tightness[5, 9-12] The most severe, systemic reaction is anaphylaxis, which can be fatal.[5, 9-12] An anaphylactic reaction can cause life-threatening airway and/or circulation problems, with respiratory arrest occurring 30 to 35 minutes after exposure to the allergen.[5, 13] One hundred and twenty-four fatalities were assessed as being highly likely to be caused by ingestion of a food allergen between 1992 and 2012 in England and Wales, and peanut allergy accounted for 16% of all cases in children under 16 years of age, and 22% of adults.[14]

Having a peanut allergy can be very stressful and negatively impact on quality of life for children due to the fear of having a potentially life-threatening allergic reaction, the need to avoid food allergens, difficulty interpreting food warning labels, and can restrict daily and social activities.[15-18] Several recent European studies have demonstrated the negative impact on quality of life associated with living with a peanut allergy, including significant emotional impact as well as disruption to daily life.[18-21] Care-giver reported quality of life of children and adolescents with peanut allergy is reported to be lower than that of the general UK young adult population.[22] Parents and caregivers can also suffer with increased stress, anxiety, disruption to daily life and careers, and lost productivity.[20, 23-25]

Current peanut allergy management relies on peanut avoidance, and rescue and emergency medication in response to allergic reaction, such as antihistamines and adrenaline auto-injection. The company state that there is an unmet need for a licensed first-line treatment option for peanut allergy. The intended place of Palforzia in the current treatment pathway is shown in Figure 6, Document B of the CS and is

reproduced by the ERG below as Figure 1. The ERG agrees that the company's description of the current treatment pathway and treatment options is accurate, and that there is currently no other licensed treatment option for desensitising individuals with peanut allergy to peanut allergens. The ERG also agrees that the company's positioning of Palforzia in the treatment pathway is appropriate.

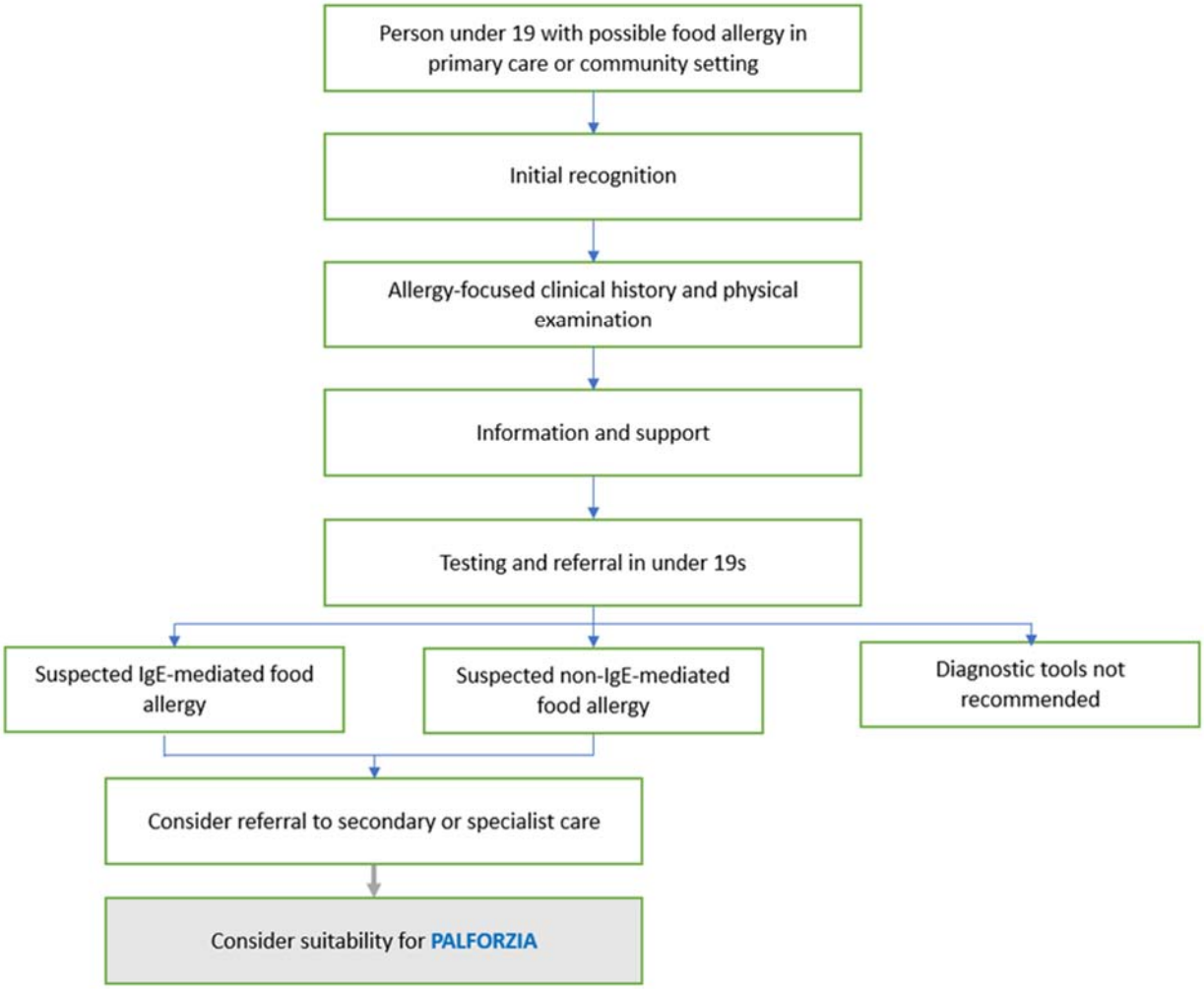


Figure 1 Proposed pathway of care of peanut allergy with Palforzia (within the NICE pathway)

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4. The ERG agrees that there are no issues regarding equality.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Children with peanut allergy aged 4 to 17 years and adults who started treatment as a child.	Patients aged 4 to 17 with a confirmed diagnosis of peanut allergy who are under the care of a specialist physician, including patients who turn 18 years old during therapy	To be in line with the final licensed indication for Palforzia (peanut protein as defatted powder of *Arachis hypogaea L*., semen (peanuts))	The CS addresses a narrower population than the population specified in the NICE final scope and focuses on patients aged 4 to 17 with a confirmed diagnosis of peanut allergy who are under the care of a specialist physician, including patients who turn 18 years old during therapy The ERG clinical expert agrees that Palforzia should only be prescribed in specialist units and is, therefore, of the opinion that population addressed in the CS is appropriate for this appraisal.
Intervention	AR101	Palforzia (peanut protein as defatted powder of *Arachis hypogaea L*., semen (peanuts))	Palforzia is the brand name for AR101	The intervention described in the CS matches that described in the NICE final scope. The final indication for Palforzia is for the treatment of patients aged

				4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older. Palforzia should be used in conjunction with a peanut-avoidant diet. Palforzia is administered orally in 3 sequential phases: Initial dose escalation, up-dosing, and maintenance. Initial dose escalation is administered in sequential order on a single day beginning at 0.5 mg and completing with 6 mg. Initial dose escalation must be completed before starting up-dosing. Up-dosing consists of 11 dose levels and is initiated at a 3 mg dose. All dose levels of up-dosing must be completed before starting maintenance. The maintenance dose of Palforzia is 300 mg daily. Daily maintenance is required to maintain the tolerability and clinical effects of Palforzia. Palforzia should be

				administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases. Palforzia was granted European marketing approval on 21st December 2020. The marketing authorisation number for Palforzia is EU/1/20/1495/008[26]
Comparator(s)	Established clinical management without Palforzia including allergen avoidance, symptomatic treatments such as antihistamines and emergency medication	As per the scope	N/A	The intervention described in the CS matches that described in the NICE final scope. The ERG clinical expert agrees with the company's description of the current UK clinical management options and prescribing patterns. The ERG, therefore, agrees that established clinical management without Palforzia (including allergen avoidance, symptomatic treatments such as antihistamines and emergency medication) is the

				appropriate comparator for this appraisal.
Outcomes	The outcome measures to be considered include: • peanut allergy desensitisation • systemic allergic reactions (including anaphylaxis) • frequency and severity of symptoms after accidental exposure to peanut • discontinuation of treatment • adverse effects of treatment • health-related quality of life.	As per the scope. It should be noted that: • Peanut allergy desensitisation, was evaluated in the clinical trials by challenge doses of <300 mg, 300 mg (443 mg cumulatively), 600 mg (1043 mg cumulatively), 1000 mg (2043 mg cumulatively) and 2000 mg (4043 mg cumulatively) peanut protein in a double-blind placebo-controlled food challenge (DBPCFC). • Allergic reactions (including anaphylaxis) and symptoms are considered separately due to treatment (safety outcome) versus due to accidental exposures to peanut (efficacy outcome).		The outcomes reported in the CS match those described in the NICE final scope. The ERG clinical expert is of the opinion that the outcomes are comprehensive and appropriate for addressing the topic of this appraisal.

		Accidental exposures to peanut requiring treatment are presented with and without the requirement of adrenaline, in line with clinical trial definitions. • As accidental exposures to peanut were relatively uncommon in the trials, data on the maximum severity of symptoms during the DBPCFC are additionally presented as a surrogate for severity of symptoms after a real-world accidental exposure to peanut. • Health-related quality of life (HRQoL) impacts are considered both for patients		

		and their caregivers.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The company have developed a *de novo* cost-effectiveness model, reporting incremental cost per QALY gained from an NHS and PSS perspective over a lifetime horizon.	Not applicable.	The ERG is satisfied that the economic analyses are consistent with the NICE scope. The ERG further critiques the economic analyses against the NICE reference case in section 4.2.1.
Subgroups	No subgroups were specified in the NICE final scope	The company conducted "supportive" analyses for the primary and "key" secondary endpoints; in PALISADE, these analyses were by geographic region (North America vs Europe) and by age group (4-11 and 12-17 years). In ARTEMIS, the analyses were by age group (4-11 and 12-17 years)	No rationale provided by the company	The ERG's clinical expert agrees that it is reasonable to explore the groups specified in the company's supportive analyses.

Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			The ERG believes there are no equity issues for this submission

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources were Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings and trial registers were also searched. Full details are provided in Appendix D.1.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, page 29: "*All identified citations had their abstracts reviewed, if available, by two independent reviewers (first pass) and any discrepancies were resolved by consensus*". At clarification, the company confirmed that two independent reviewers conducted full text screening
Was data extraction conducted by two or more reviewers independently?	No	Appendix D, page 29: "*Extractions were performed by one reviewer using a*

		standardised data extraction form and checked for accuracy by a second reviewer"
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	The CS does not specify which criteria were used but it appears to be the University of York Centre for Reviews and Dissemination checklist
Was risk of bias assessment conducted by two or more reviewers independently?	Yes	At clarification, the company confirmed that two independent reviewers conducted the full text screening
Was identified evidence synthesised using appropriate methods?	Partially	No meta-analyses were attempted, although this would have been possible. The economic modelling primarily used patient-level data from one study instead of pooling data from multiple studies. The ERG agrees with this approach but could not find clear justification why certain studies had been excluded

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Note. Steps 3, 4 and 5 were not conducted by the company for ARC001

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Document B, Section B.2 of the CS.

Efficacy analyses

Four RCTs were identified by the company's literature review: the CS included mainly data from PALISADE (ARC003) and its follow-on study ARC004, with ARTEMIS (ARC010) as a sensitivity analysis. RAMSES (ARC007) was not included in the company's efficacy analyses as no efficacy analyses were conducted. The ERG agrees that its exclusion is appropriate. A Phase 2 RCT (ARC001) was also identified by the company's literature review. The company's rationale for not including ARC001 was that it was conducted solely in the USA and was of small sample size (n=55). The ERG is of the opinion that ARC001 meets the inclusion criteria and was eligible for inclusion. However, the ERG agrees that its inclusion would be unlikely to make a major difference to the conclusions about the efficacy of Palforzia. The ERG report considers ARC001 alongside PALISADE, ARC004 and ARTEMIS for the sake of comparison and completeness.

Safety analyses

Main modelling used PALISADE, ARC004 and ARTEMIS. Pooled data from PALISADE, RAMSES, ARTEMIS and their respective follow-on studies are described in the CS (Document B, Section 2.10.3). At least one analysis (Document B, Section 2.10.3, Figure 22) also uses data from ARC008, a follow-on study with participants from the above three studies plus ARC001. Details of the three trials included in the CS are summarised in Table 4, Section B.2.2, Document B and an amended version including details of ARC001 is presented as Table 6 below.

Table 6 Clinical effectiveness evidence [amended from Table 4, Section B.2.2, Document B of the CS]

Study	ARC003 (PALISADE), NCT02635776	ARC004 (PALISADE follow-on), NCT02993107	ARC010 (ARTEMIS), NCT03201003	*ARC001, NCT01987817
Study design	Phase 3 international, randomised, double-blind, placebo-controlled trial	Open-label follow-on study of the Phase 3 PALISADE study	Phase 3 international, randomised, double-blind placebo-controlled trial	Phase 2, randomised, double-blind, placebo-controlled trial
Population	Participants aged 4 to 55 years with a clinical history of allergy to peanuts or peanut-containing foods	Participants aged 4 to 55 years who completed the PALISADE (ARC003) study	Participants aged 4 to 17 years with a clinical history of allergy to peanuts or peanut-containing foods	Participants aged 4 to 26 years with a clinical history of peanut allergy
Intervention(s)	Palforzia + avoidance	Palforzia + avoidance	Palforzia + avoidance	Palforzia + avoidance
Comparator(s)	Placebo + avoidance	Not applicable	Placebo + avoidance	Placebo + avoidance
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes	No. ARC001 meets the study inclusion criteria but was not included due to its small sample size and being located in the USA. The ERG agrees that ARC001 may not provide further meaningful clinical effectiveness evidence to the CS
Indicate if trial used in the economic model	Yes (patients aged 4-17 only)	Yes (patients aged 4-17 at beginning of ARC003,	Yes	No

		once daily dosing, Cohorts 1 and 3A only)		
Rationale for use/non-use in the model	PALISADE is a pivotal clinical trial supporting the EMA regulatory submission and the approved indication for Palforzia. The trial provides comparative evidence for Palforzia versus placebo	This follow-on trial provides information on safety and sustained efficacy and supports the EMA regulatory submission, as per the SmPC. The trial provides longer term data and confirms the long-term efficacy of daily dosing.	ARTEMIS is a pivotal clinical trial supporting the EMA regulatory submission and the approved indication for Palforzia. The trial provides comparative evidence for Palforzia versus placebo	N/A
Reported outcomes specified in the decision problem ***Bold outcomes are included in the base case economic model***	• **Peanut allergy desensitisation** • **Systemic allergic reactions (including anaphylaxis)** • **Frequency and severity of symptoms after accidental exposure to peanut** • **Treatment discontinuation** • **Adverse effects (AEs) of treatment** • Health-related quality of life	• **Adverse effects (AEs) of treatment** • **Peanut allergy desensitisation** • **Systemic allergic reactions (including anaphylaxis)** • Frequency and severity of symptoms after accidental exposure to peanut • **Treatment discontinuation** • Health-related quality of life	• **Peanut allergy desensitisation** • **Systemic allergic reactions (including anaphylaxis)** • **Frequency and severity of symptoms after accidental exposure to peanut** • **Treatment discontinuation** • **Adverse effects (AEs) of treatment** • Health-related quality of life	• **Peanut allergy desensitisation**
All other reported outcomes	Efficacy outcomes: • The maximum symptom severity in participants	Efficacy outcomes:	Efficacy outcomes: • The maximum symptom severity that occurred at	Efficacy outcomes

	aged 4 to 17 years that occurred at any challenge dose of peanut protein during the exit DBPCFC • The proportion of participants aged 18 to 55 years who tolerated a single highest dose of at least 1000 mg of peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC • Maximum dose achieved with no or mild symptoms at exit • The change from baseline in single highest tolerated dose of peanut protein at DBPCFCs • The use of adrenaline as rescue medication at the exit DBPCFC • Changes in peanut-specific serum IgE and IgG4 levels	• The use of adrenaline as rescue medication • Single highest tolerated dose and change from baseline at the maintenance and exit DBPCFCs • Maximum severity of symptoms at each challenge dose at the maintenance and exit DBPCFCs • Treatment satisfaction as assessed by the TSQM-9 questionnaire • Changes in peanut-specific IgE and IgG4 levels • Changes in peanut skin prick test wheal diameter Safety outcomes: • Assessment of asthma control using the Asthma Control Test questionnaire in participants with asthma	any challenge dose of peanut protein during the exit DBPCFC • Maximum dose achieved with no or mild symptoms at exit • The change from baseline in single highest tolerated dose of peanut protein at DBPCFCs • The use of adrenaline as rescue medication at the exit DBPCFC • Changes in peanut-specific serum IgE and IgG4 levels • Changes in peanut skin prick test diameter • Treatment satisfaction as assessed by the TSQM-9 questionnaire and exit questionnaire • Use of adrenaline as rescue medication during initial dose escalation, up-dosing and maintenance (by age group)	• Maximum dose achieved with no or minimal symptoms • Change in maximum tolerated dose from screening to exit DBPCFC • Change from baseline in peanut-specific IgE and IgG4 serum and peanut SPT wheal diameter Safety outcomes • Adverse event rates

	• Changes in peanut skin prick test diameter • Treatment satisfaction as assessed by the TSQM-9 questionnaire Safety outcomes: • Assessment of asthma control using the Asthma Control Test in participants with asthma (by age group)		Safety outcomes: • Assessment of asthma control using the Asthma Control Test in participants with asthma (by age group)	

AE: adverse events; DBPCFC: double-blind placebo-controlled food challenge; EMA: European Medicines Agency; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy-Related Quality of Life Questionnaire; IgE: immunoglobulin E; IgG4: immunoglobulin G4; NHLBI; SmPC: Summary of Product Characteristics; TSQM-9: Treatment Satisfaction Questionnaire for Medication. Note: since accidental exposure to peanuts is a rare occurrence, the maximum severity of symptoms occurring during the exit DBPCFC is used as a surrogate endpoint
*ARC001 was not included in the CS but is reported here merely for comparison

Details of PALISADE, ARC004 and ARTEMIS are reported in sections B.2.2 and B.2.3 of the CS. Participant flows of the studies are presented in Section D1.3, Appendix D of the CS. All three trials were funded by Aimmune Therapeutics. PALISADE was conducted at 66 sites in 10 countries, ARC004 at 65 sites in nine countries and ARTEMIS at 18 sites in seven countries. All trials recruited participants in the UK (PALISADE: number of UK participants not reported; ARC004: [redacted] in cohort 1, [redacted] in cohort 3A; ARTEMIS: [redacted] of active treatment group, [redacted] of placebo group). The methods used in PALISADE and ARTEMIS were similar. Participants were randomly assigned in a 3:1 ratio to Palforzia or placebo, in a dose-escalation study comprising three phases: the two-day dose escalation phase involved escalating doses of Palforzia (0.5mg to 6mg) or placebo; the up-dosing phase, in which doses of Palforzia were increased at two-week intervals from 3mg/day to 300mg/day over 20-40 weeks (PALISADE) or up to 40 weeks (ARTEMIS); the maintenance phase, with participants receiving 300mg/day of the study drug for 24-28 weeks (PALISADE) or 12 weeks (ARTEMIS). Full details of the dosing regimens in the included studies were reported in the CS (Table 4, Document B).

The ARC001 trial was conducted at eight centres in the USA and was funded by Aimmune Therapeutics. Participants were randomised in a 1:1 ratio to Palforzia or placebo. Study methods were similar to those of PALISADE and ARTEMIS, with the final dose of 300mg/day occurring over 20 to 34 weeks.

The study population in PALISADE, ARTEMIS and ARC001 was people with a clinical history of allergy to peanuts or peanut-containing foods aged 4 to 55 years (PALISADE), 17 years (ARTEMIS) or 26 years (ARC001). Protocol modifications for the PALISADE trial included changing the upper limit of the eligible age range from 55 years to 17 years for primary and secondary objectives. The company's rationale for this change was "[redacted]". Accordingly, only data from

participants in the 4 to 17 years age group were used to populate the economic model. In addition, the company changed the primary efficacy endpoint for Europe from tolerating a single highest dose of at least 600 mg to 1000 mg of peanut protein in line with the fact that the "[redacted]". The primary efficacy endpoint was tolerating 1000mg peanut protein in PALISADE and ARTEMIS. The main inclusion and exclusion criteria of PALISADE, ARTEMIS and ARC001 were comparable.

The ARC004 trial is an open-label extension to PALISADE. In brief, eligible participants were those from the Palforzia arm of PALISADE who could tolerate 300mg of peanut protein at the exit DBPCFC and those from the placebo arm. Of the total five assessed cohorts, the economic model used the two which involved daily use of 300mg Palforzia treatment for either 28 weeks (Cohort 1) or approximately 56 weeks (Cohort 3A). The primary outcome of ARC004 was incidence of [redacted] AEs, defined as "[redacted]"

The criteria used to assess the risk of bias of the main sources of evidence (i.e., PALISADE, ARC004 and ARTEMIS studies) were not specified in the CS but appear to be those of the Centre for Reviews and Dissemination checklist for RCTs.[27] The ERG broadly agrees with the company's assessments. ARC004 was an open-label study and at high risk of the bias inherent in this study design. Both PALISADE and ARTEMIS were well-conducted randomised, double-blind trials and the ERG considers that risk of bias of these studies to be low for most domains. The CS did not report risk of bias

for ARC001 so the ERG conducted an assessment based on the criteria used for the included studies. ARC001 was described as “double blind” but it was unclear exactly who was blinded and there was a slight imbalance in the groups for atopic dermatitis/eczema at baseline. In general, though, the ERG is of the opinion that risk of bias in ARC001 was low. In ARC004, arms 3a, 3b and 3c involved randomisation but only groups 1 and 3a were included in the model as they remained on daily dosing as for the Palforzia labelled indication.

The CS presents details of baseline characteristics separately for each trial (Tables 8, 10 and 13 of Document B); these are summarised in Table 7 below along with details of ARC001. As the two cohorts of interest in ARC004 both received Palforzia and the trial was open label, the balance of characteristics across the groups is not of concern. In general, baseline characteristics were balanced within PALISADE but less so within ARTEMIS. Median age ranged from [redacted] years (Palforzia group, ARTEMIS) to 11 years (Cohort 1, ARC001). The proportion of males and females were mostly within the arms of trials, with the exception of the placebo arms of PALISADE (61.3% males) and ARTEMIS (62.8% males). In PALISADE and ARC004, the majority of participants were in North America or the USA, respectively, whilst recruitment in ARTEMIS was solely in European countries. Median peanut specific IgE levels at baseline were balanced across the Palforzia and placebo groups in PALISADE ([redacted] and [redacted] kUA/L, respectively) but higher in the placebo (69.70 kUA/L) than the Palforzia group (43.50 kUA/L) of ARTEMIS. Prick test wheal diameter was balanced within PALISADE and ARTEMIS, albeit higher in both groups of PALISADE ([redacted] and [redacted] mm in the Palforzia and placebo groups, respectively) than ARTEMIS (9.50 and 9.75 mm, respectively). Non-peanut allergy history was balanced across the groups in PALISADE but there was a tendency for the Palforzia arm of ARTEMIS to have higher incidence of the specified allergies. Baseline characteristics were generally balanced across the randomised groups in ARC001, although the median peanut-specific IgE in the placebo group was at the upper limit of quantification of 100kUA/L. Overall, participants in ARC001 were similar to those in PALISADE and ARTEMIS.

The ERG's clinical expert is satisfied that the baseline characteristics of the participants in PALISADE, ARTEMIS and ARC001 are representative of patients seen in clinical practice in the UK.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures to be considered, as specified in the NICE final scope were: peanut allergy desensitisation, systemic allergic reactions (including anaphylaxis), frequency and severity of symptoms after accidental exposure to peanut, discontinuation of treatment, adverse effects of treatment and health-related quality of life. The included trials utilised a surrogate outcome to assess tolerance: a double-blind placebo-controlled food challenge (DBPCFC) which simulates accidental exposure to peanut. The ERG agrees with the company's assertion that the DBPCFC is the gold standard for diagnosing food allergies and, as the only available validated measure of efficacy of oral immunotherapy in clinical settings, is accepted by regulatory agencies as an appropriate endpoint. In summary, the DBPCFC involves gradually increasing doses of the pertinent allergen (in this case, peanut protein) being administered in a single visit in a medically supervised setting, continuing until an allergic reaction is elicited. This procedure is repeated with peanut protein and an equivalent placebo (oat flour) on separate days and in random order. In PALISADE, ARC004 and ARTEMIS, the DBPCFC was performed according to modified PRACTALL guidelines at screening and exit.[28] The company modified the standard DBPCFC protocol to include a peanut protein dose of 600mg during the exit DBPCFC. Full details of the timing and doses of the DBPCFC are presented in the CS (Document B, Table 6) and reproduced as Table 8 below.

Table 7 Baseline characteristics of participants in PALISADE, ARC004, ARTEMIS and ARC001 [adapted from Tables 8, 10 and 13, Document B of the CS]

	PALISADE		ARC004		ARTEMIS		*ARC001	
	Palforzia (N=372)	**Placebo (N=124)**	**Cohort 1 (N=112)[a]**	**Cohort 3A (N=31)[a]**	**Palforzia (N=132)**	**Placebo (N=43)**	**Palforzia (N=29)**	**Placebo (N=26)**
Age, years								
Median	9.0	9.0	11.0	9.0	[redacted]	[redacted]	7	8
4 to 11 years, n (%)	238 (64.0)	89 (71.8)	[redacted]	[redacted]	97 (73.5)	30 (69.8)	NR	NR
12 to 17 years, n (%)	134 (36.0)	35 (28.2)	[redacted]	[redacted]	35 (26.5)	13 (30.2)	NR	NR
Sex								
Male, n (%)	208 (55.9)	76 (61.3)	57 (52.3)	17 (54.8)	68 (51.5)	27 (62.8)	20 (69.0)	16 (61.5)
Geographic region								
USA	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	29 (100)	26 (100)
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)
UK	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)
Peanut specific IgE (kUA/L)								
Median (Q1, Q3)	[redacted]	[redacted]	63.5 (20.9, 247.5)[b]	45.4 (2.73, 220.5)[b]	43.50 (5.20, 147.00)[d]	69.70 (20.70, 103.00)	64.3 (range 0.8 to ≥100)	100.0 (range 3.5 to ≥100)
Prick test wheal diameter (mm)								

	PALISADE		ARC004		ARTEMIS		*ARC001	
	Palforzia (N=372)	**Placebo (N=124)**	**Cohort 1 (N=112)[a]**	**Cohort 3A (N=31)[a]**	**Palforzia (N=132)**	**Placebo (N=43)**	**Palforzia (N=29)**	**Placebo (N=26)**
Median (Q1, Q3)	[redacted]	[redacted]	7.5 (5.5-10.0)[c]	7.0 (4.0-9.5)[c]	9.50 (7.50, 12.25)[e]	9.75 (8.00, 12.50)[f]	14 (range 5-30)	13 (5-26)
Non-peanut allergy history								
Allergic rhinitis, n (%)	[redacted]	[redacted]	79 (72.5)	20 (64.5)	63 (47.7)	16 (37.2)	18 (62.1)[g]	18 (69.2)[g]
Asthma, n (%)	[redacted]	[redacted]	47 (43.1)	14 (45.2)	56 (42.4)	14 (32.6)	12 (41.4)	11 (42.3)
Atopic dermatitis, n (%)	[redacted]	[redacted]	67 (61.5)	22 (71.0)	78 (59.1)	22 (51.2)	19 (65.5)[h]	11 (42.3)[h]
Other food allergy, n (%)	[redacted]	[redacted]	67 (61.5)	17 (54.8)	81 (61.4)	21 (48.8)	7 (24.1)[i]	4 (15.4)[i]

Note. [a]Percentage of age categories NR in CS. Percentages reported for sex, geographic region, non-peanut allergy history are presented in this table as reported in CS and CSR, which use the safety population as the denominator (i.e. n=109 and 31 for Cohorts 1 and 3A, respectively); [b]Reported in CSR as [redacted] and [redacted], respectively; [c]Reported in CSR as [redacted] and [redacted], respectively; [d]N=126; [e]N=128; [f]N=43; [g]Reported as allergic rhinitis/hayfever; [h]Reported as atopic dermatitis/eczema; [i]Reported as other allergy, including food or drug allergy; *ARC001 was not included in the CS but is reported here merely for comparison

Abbreviations. NR: not reported, IgE: immunoglobulin E, Q: quartile

Table 8 Modified PRACTALL DBPCFC doses using peanut flour with 50% peanut protein content at screening and exit DBPCFC [reproduced from Document B, Table 6 of the CS]

	Challenge doses (administered at 20–30-minute intervals)		
	Amount of peanut protein at each challenge dose (mg)	**Cumulative amount of peanut protein (mg) at Screening**	**Cumulative amount of peanut protein (mg) at Exit**
Screening only*	1	1	0 (or 1)*
Screening and Exit	3	4	3 (or 4)*
Screening and Exit	10	14	13 (or 14)*
Screening and Exit	30	44	43 (or 44)*
Screening and Exit	100	144	143 (or 144)*
Exit only	300	-	443 (or 444)*
Exit only	600	-	1043 (or 1044)*
Exit only	1000	-	2043 (or 2044)*
Exit only†	2000	-	4043 (or 4044)*

*Participants who failed their Screening DBPCFC at the 1-mg challenge dose of peanut protein were required to start the Exit DBPCFC with a 1-mg dose. At the investigator's discretion, a 1-mg dose could be added at the beginning of the escalation of any participant's Exit DBPCFC.
†The 2000-mg dose was only used in ARC004

Primary endpoint: Peanut allergy desensitisation

The primary endpoint of PALISADE and ARTEMIS was peanut allergy desensitisation, defined as the proportion of participants who tolerated a single highest dose of at least 1000mg of peanut protein (2043mg cumulative) without dose-limiting symptoms. This outcome was also reported in the CS for ARC004, albeit not a primary outcome for that particular study (see Table 9). The primary endpoint was met in the respective ITT populations of both PALISADE and ARTEMIS. In PALISADE, the desensitisation response rates were 50.3% in the Palforzia arm (n=372) versus 2.4% for the placebo arm (n=124), with a treatment difference (Palforzia-placebo) of 47.8% (95% CI 38.0, 57.7; p<0.0001). In ARTEMIS, the desensitisation response rates were 58.3% in the Palforzia arm (n=132) and 2.3% in the placebo arm (n=43), the treatment difference being 56.0% (95%CI 44.2, 65.2; p<0.0001). In ARC001, 18/29 (62.1%) of the Palforzia group and 0/26 (0.0%) of the placebo group tolerated 1043mg at the exit DBPCFC (see Table 9).

In addition to the primary endpoint relating to peanut allergy desensitisation, the CS further reported proportions of participants who tolerated at least 600mg and 300mg of peanut protein as “key” secondary outcomes. Both of these endpoints were met by the ITT populations in PALISADE and ARTEMIS.

The CS also reported peanut allergy desensitisation for the completer populations of Cohorts 1 and 3A of ARC004 (i.e., participants receiving maintenance treatment of 300mg Palforzia daily). Outcomes reported in the CS and ARC001 in relation to peanut allergy desensitisation are presented in Table 9.

Table 9 Summary of primary and selected secondary endpoints for PALISADE, ARC004, ARTEMIS and ARC001

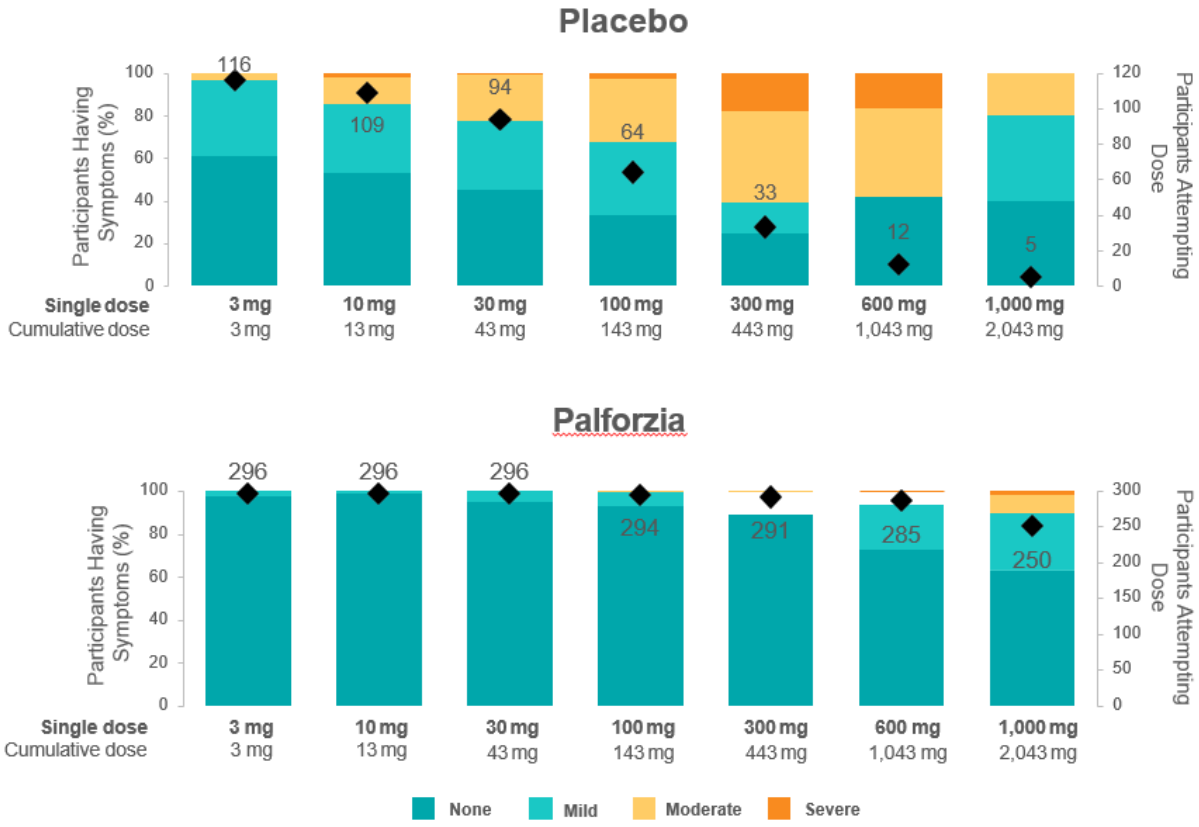
	PALISADE		ARC004		ARTEMIS		*ARC001	
	Palforzia (n=372)	**Placebo (n=124)**	**Cohort 1 (n=103)[a]**	**Cohort 3A (n=26)[a]**	**Palforzia (n=132)**	**Placebo (n=43)**	**Palforzia (n=29)**	**Placebo (n=26)**
Tolerance of 1000mg, % (95%CI)	50.3 (45.2, 55.3)	2.4 (0.8, 6.9)	80.6 (71.6, 87.7)	96.2 (80.4, 99.9)	58.3 (49.4, 66.8)	2.3 (0.1, 12.3)	NR	NR
Treatment difference (Palforzia-placebo), %	47.8 (38.0, 57.7), p<0.0001		NR		56.0 (44.1, 65.2), p<0.0001		NR	
Tolerance of 600mg, % (95%CI)	67.2 (62.3, 71.8)	4.0 (1.7, 9.1)	89.3 (81.7, 94.5)	96.2 (80.4, 99.9)	68.2 (59.5, 76.0)	9.3 (2.6, 22.1)	62.1	0.0
Treatment difference (Palforzia-placebo), %	63.2 (53.0, 73.3), p<0.0001		NR		58.9 (44.2, 69.3), p<0.0001		NR p<0.0001	
Tolerance of 300mg, % (95%CI)	76.6 (72.1, 80.6)	8.1 (4.4, 14.2)	98.1 (93.2, 99.8)	100 (86.8, 100)	73.5 (65.1, 80.8)	16.3 (6.8, 30.7)	79.3	19.2
Treatment difference (Palforzia-placebo), %	68.5 (58.6, 78.5), p<0.0001		NR		57.2 (41.2, 69.1), p<0.0001		NR	
Maximum severity of symptoms at any dose during exit DBPCFC, n (%)								
None	[redacted]		51 (49.5)[b]	18 (69.2)[b]	[redacted]		NR	NR
Mild	[redacted]		30 (29.1)[b]	7 (26.9)[b]	[redacted]		NR	NR
Moderate	[redacted]		20 (19.4)[b]	1 (3.0)[b]	[redacted]		NR	NR
Severe or higher	[redacted]		2 (1.9)[b]	0[b]	[redacted]		NR	NR
P-value	[redacted]		NR		[redacted]		NR	NR

Note. [a]Completer population; [b]At any challenge dose, 2000mg or lower; NR: not reported; *ARC001 was not included in the CS but is reported here merely for comparison

Other endpoints

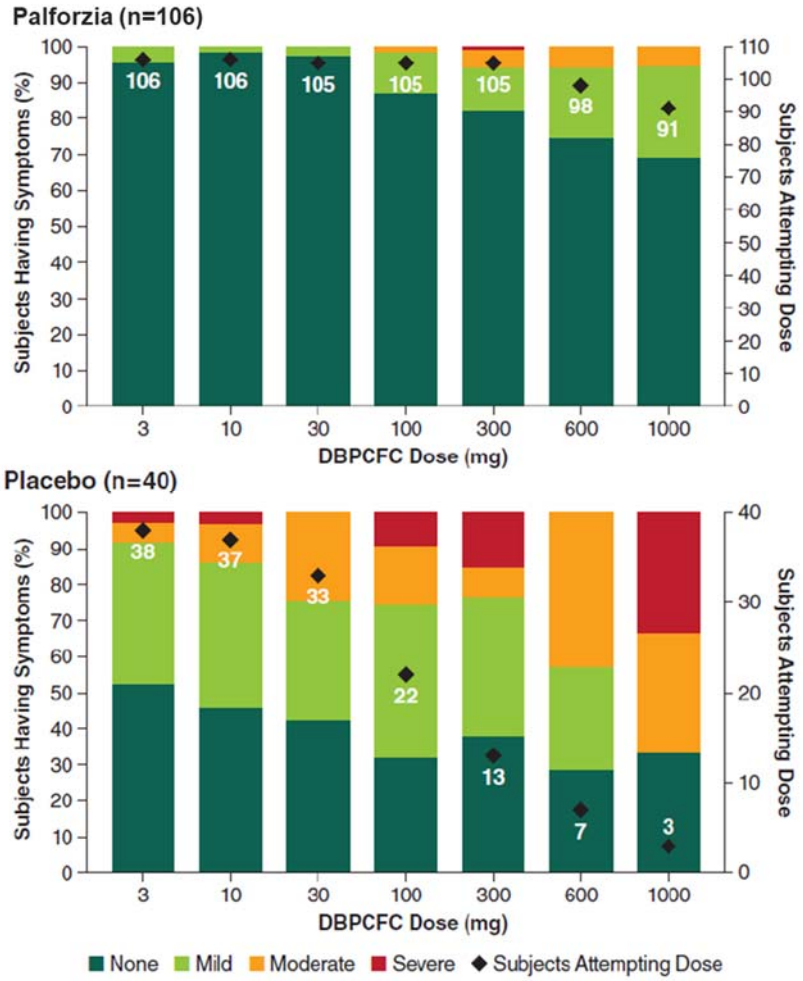
Other efficacy endpoints reported in the CS are as follows:

- **Frequency and severity of symptoms after accidental exposure to peanut**: referred to by the company as 'accidental exposure to peanut requiring treatment with and without adrenaline'. The CS reports maximum severity of symptoms at any challenge dose of peanut protein during the exit DBPCFC as a surrogate endpoint, due to the uncommon nature of accidental exposure to peanut. Accidental exposure to peanut was low during the maintenance phases of both PALISADE ([redacted] and [redacted] in the Palforzia and placebo groups, respectively) and ARTEMIS ([redacted] and [redacted] respectively). Of these, [redacted] of the Palforzia group and [redacted] of the placebo group in PALISADE experienced an adverse event (AE) requiring treatment. Requirement for adrenaline use for accidental peanut exposure was low in both groups ([redacted] and [redacted] respectively). In ARTEMIS, [redacted] needed treatment or adrenaline following accidental peanut exposure. Maximum severity of symptoms at any challenge dose during the exit DBPCFC are presented in Table 9 above. Results were broadly similar across PALISADE and ARTEMIS with [redacted] participants in the Palforzia groups having 'none' or 'mild' symptoms at maximum, whilst [redacted] of placebo-treated participants experienced 'moderate' symptoms. [redacted] participants in both placebo groups experienced 'severe or higher' symptoms ([redacted] in PALISADE and [redacted] in ARTEMIS) than those treated with Palforzia ([redacted] and [redacted] respectively). Maximum severity of symptoms occurring during each dose of the exit DBPCFC of the completer populations are presented in the CS for PALISADE (Figure 14, Document B) and ARTEMIS (Figure 19, Document B) and are reproduced as Figure 2 and Figure 3 below.



DBPCFC: double-blind, placebo-controlled food challenge.
Bars are measured on the primary Y-axis and diamonds are measured on the secondary Y-axis.
Source: Adapted from Vickery et al. 2018[29]

Figure 2 PALISADE (ARC003) maximum severity of symptoms occurring during each dose of the exit DBPCFC with peanut among participants aged 4 to 17 years (completer population) [reproduced from Figure 14, Document B of the CS]



DBPCFC: double-blind, placebo-controlled food challenge
Bars are measured on the primary Y-axis and points are measured on the secondary Y-axis.
Source: Hourihane et al. 2020[30]

Figure 3 ARTEMIS Maximum severity of symptoms occurring during each dose of the exit DBPCFC among participants aged 4 to 17 years (completer population) [reproduced from Figure 19, Document B of the CS]

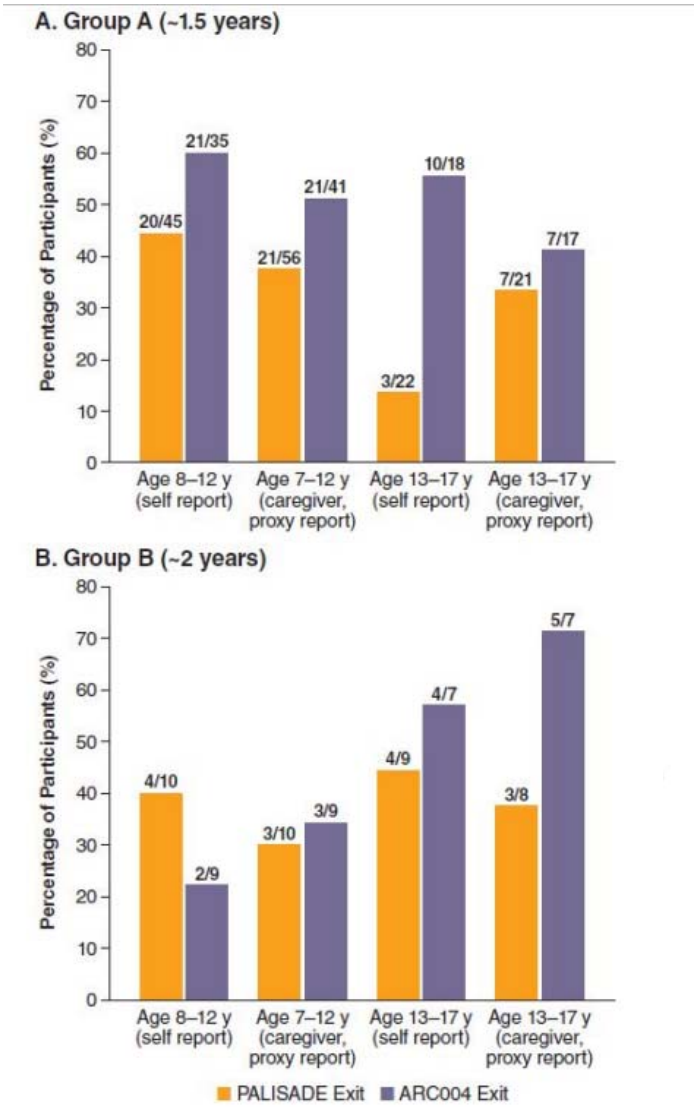
Rates of accidental food allergen exposure were higher in ARC004 than in PALISADE or ARTEMIS: [redacted] in Cohort 1 and [redacted] in Cohort 3A. The CS reported that the rates of accidental exposure to peanut requiring treatment were [redacted] in Cohort 1 and [redacted] in Cohort 3A and that [redacted] required adrenaline for accidental peanut exposure. The ERG notes that Table 63 of the ARC004 CSR reports that [redacted] of Cohort 1 and [redacted] of Cohort 3A required treatment and [redacted] and [redacted] respectively, required epinephrine use for accidental exposure to peanut.

- **Discontinuation of treatment:**
  The CS reports that a total of 11.4% of the integrated safety population (i.e., participants aged 4 to 17 years who received at least one dose of Palforzia during PALISADE, ARTEMIS, a further Phase 3 trial [RAMSES] and/or two follow-on studies: ARC004 and ARC011; n=944) discontinued Palforzia due to an adverse reaction. Of these, three participants discontinued Palforzia due to anaphylaxis (severe anaphylactic reaction).

  The ERG noted some discrepancies in the reporting of discontinuations from the three studies between the CS and the respective CSRs. The CS (Appendices, Section D1.3) reports that, in PALISADE, there were 43 (11.6%) withdrawals from the Palforzia group and 3 (2.4%) withdrawals from the placebo group due to AEs. Of these, 6.5% in the Palforzia group and 1.6% in the placebo group were for acute/chronic/recurrent GI (Table S7, Supplementary Appendix, Vickery 2018[29]). The ERG notes that Figure 2 of the PALISADE CSR shows that 34/80 participants who discontinued in the Palforzia arm and 2/10 discontinuations in the placebo arm were due to AEs.[31] For ARTEMIS, the CS reports 15/26 and 1/3 participants who discontinued the study in the Palforzia and placebo arms, respectively, being due to AEs. The ARTEMIS CSR (Figure 2, page 56) reports that 14/26 and 1/3 of participants who discontinued were due to AEs.[31] The CS reports that 2/7 and 1/5 participants who discontinued in Cohorts 1 and 3A of ARC004, respectively, were as a result of AEs. The ARC004 CSR (Figure 2, page 57) reports that 2/10 and 1/5, respectively, of those who discontinued were for AEs.[32] Six participants in the Palforzia arm of ARC001 discontinued the study, four of these due to adverse events, primarily recurrent gastrointestinal-related.

- **Health-related quality of life:** Disease-specific HRQoL was assessed in the three trials using the Food Allergy-Related Quality of Life Questionnaire (FAQLQ) and the Food Allergy Independent Measure (FAIM). Both scales were completed by participants aged 8 to 12 years and 13 to 17 years (i.e., self-report) and by caregivers of all participants

(i.e., proxy report). Reduction in scores represents an improvement in HRQoL for both the FAQLQ and the FAIM. For the FAQLQ, the overall minimal important difference is around 0.5. Full results of the HRQoL are reported in the CS (Document B, Section 2.6.4). In PALISADE, there [redacted] In ARTEMIS, [redacted] from baseline to study exit, with the exception of self-reported FAQLQ total score in 8 to 12 year olds, in which the difference in scores (Palforzia-placebo) demonstrated a statistically significant and clinically meaningful improvement of -1.09 (95%CI -1.95, -0.22; p=0.0154). Changes in FAIM scores between baseline and study exit were variable across domains; the difference (Palforzia-placebo) in change in total scores reported by parents for children aged 4 to 12 years was [redacted] but, in general, there were no other statistically significant or clinically meaningful improvements. For ARC004, FAQLQ and FAIM were reported in terms of change from baseline, defined as day 1 of PALISADE, to ARC004 exit. The majority of self-reported and parent proxy-reported FAQLQ and FAIM scores showed improvements from baseline at the MID (i.e., 0.5) in both Cohort 1 and Cohort 3A. The CS presents a post-hoc exploration of FAQLQ scores in Cohorts 1 (“Group A”) and 3A (“Group B”) of ARC004 (Document B, Figure 21), demonstrating scores at PALISADE exit and ARC004 (reproduced as Figure 4 below).



FAQLQ: Food Allergy Quality of Life Questionnaire
Group A is equivalent to ARC004 Cohort 1 and Group B is Cohort 3A
Source: Fernandez-Rivas et al., 2021

Figure 4 PALISADE follow-on (ARC004) FAQLQ responder analysis (percentage of participants whose FAQLQ total score reduced [i.e., improved] by 0.5 points from PALISADE baseline to ARC004 exit) [reproduced from Figure 21, Document B of the CS]

3.2.3 Subgroup analysis

No subgroups were specified in the NICE final scope. The CS reports "supportive analyses" for the primary and "key" secondary endpoints in the ITT and completer populations of PALISADE (i.e., those of the ITT population who completed treatment and had an evaluable exit DBPCFC) and the primary endpoint in the ARTEMIS ITT population.

In PALISADE, the supportive analyses to the primary endpoint were: by geographic region (North America and Europe), by age group (4-11 years and 12-17 years) and by geographic region and age group (North America 4-11 years, North America 12-17 years, Europe 4-11 years, Europe 12-17 years). In ARTEMIS, the supportive analysis to the primary endpoint were by age group (4-11 years and 12-17 years) and by country. The ERG's clinical expert is satisfied that these groups are reasonable in terms of subgroup or supportive analyses. Results of the analyses are reported in the CS (Document B, Section B.2.7) and [redacted]. For the primary efficacy endpoint in PALISADE, the difference between Palforzia and placebo was [redacted] for both Europe and North America and for the 4 to 11 years and 12 to 17 years groups. When considering the regional and age groups combined, all combinations remained [redacted], with the exception of the 12 to 17 years group in Europe. In ARTEMIS, the difference between Palforzia and placebo was [redacted] for both the 4 to 11 years and 12 to 17 years groups.

3.2.4 Adverse reactions

The company conducted their systematic review of efficacy and safety in line with current methodological standards. Details of the review methods are reported in Appendix F of the CS. However, the ERG notes that the way the company presents safety data in section B.2.10 of the CS lacks transparency and is not consistent with the use of safety data in the company's cost-effectiveness model. Safety was assessed in the PALISADE, ARC004, and ARTEMIS trials and, while all-cause treatment emergent adverse events (TEAEs) are reported as the focus of the safety analyses in the clinical effectiveness side of the CS, only treatment-related adverse events (TRAEs) during the up-dosing and maintenance phases of PALISADE and the ARC004 extension study are used in the company's cost-effectiveness model. Adverse reactions due to accidental exposure to peanut are included in the model separately to TRAEs, as an indicator of treatment efficacy rather than safety. The ERG provides a critique of the company's economic model in Chapter 4.

TEAEs are defined as all-cause adverse events occurring after the first dose of the study intervention, and which may or may not be related to the study intervention. TRAEs are defined as a subset of TEAEs related specifically to treatment as determined by the clinical judgement and expertise of the study investigator to be related to the study intervention. The investigator was blinded to whether the subject has taken active product or placebo at the point of determination. The ERG is satisfied that the methods used to determine TRAEs are appropriate.

The majority of TEAEs were either mild or moderate. There was one case of severe anaphylaxis in the active-drug group during the maintenance phase of the PALISADE trial, and no severe anaphylaxis cases in the ARTEMIS trial.

The company reports pooled safety data for the integrated safety population, which included all participants aged 4 to 17 years receiving at least one dose of Palforzia during PALISADE, ARTEMIS and RAMSES, in Table 26 of the CS, and reproduced by the ERG as Table 10. The safety data of placebo participants were not included in the integrated safety population. Data for ARC004 and ARC011 trials were included up to the data cut-off date of 15 December 2018.[33, 34] An additional analysis of the pooled safety population including the ongoing ARC008 trial (data cut-off July 31, 2020) is also presented in Figure 22 of the CS, and reproduced by the ERG as Figure 5.[35] The ERG notes some concerns around the transparency of study selection in reporting the pooled safety data in the CS. PALISADE and ARC004 are used in the company's economic modelling, but in B2.10.2 safety data are described for PALISADE, ARC004 (Cohorts 1 and 3A) and ARTEMIS, while Table 26 additionally includes RAMSES and ARC011, and Figure 22 additionally includes TRAEs data for ARC008 (including ARC001 data).

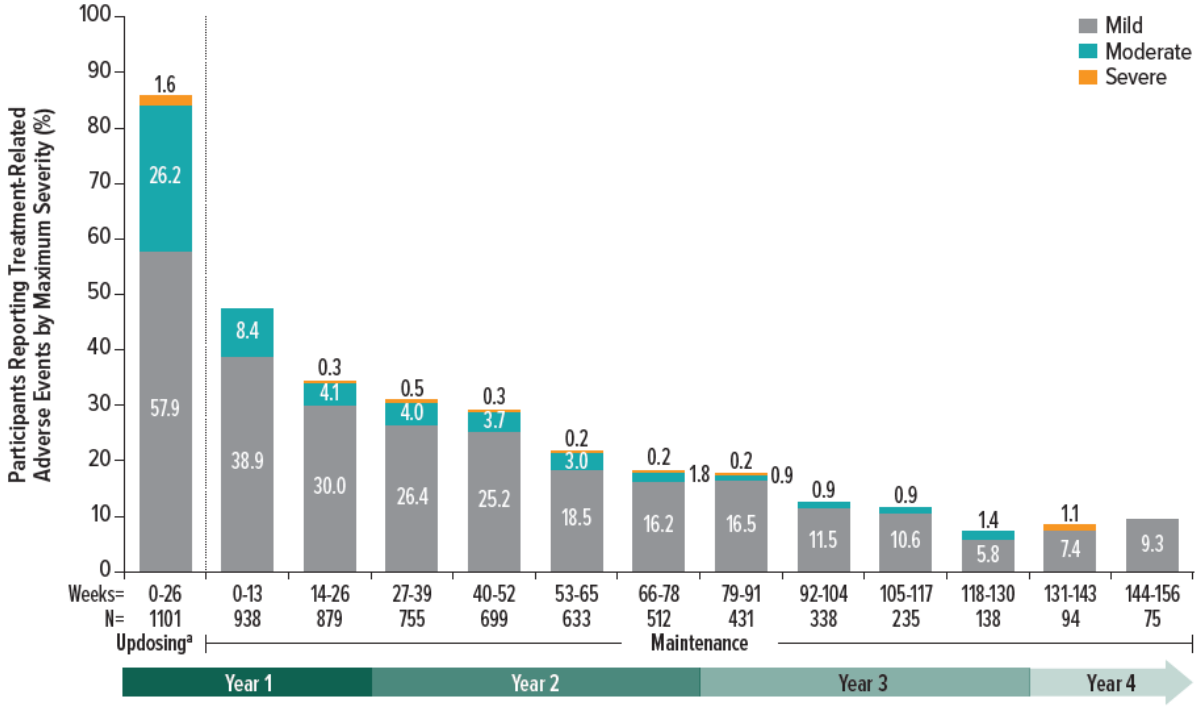
The pooled safety data indicate that the incidence of TEAEs was higher during up-dosing phase (85.7%) but both incidence and severity declined during maintenance treatment. Most adverse reactions to Palforzia were mild to moderate and in keeping with the safety profile of Palforzia and an oral

mode of administration of treatment. TRAEs experienced by ≥10% of the integrated safety population during the 300mg/day dosing are presented in Table 18, Appendix F of the CS. Treatment discontinuation of Palforzia due to ≥1 adverse reaction occurred in 11.4% of participants. The most common adverse reactions leading to discontinuation of treatment were abdominal pain (3.8%), vomiting (2.5%), nausea (1.9%), and anaphylactic reaction (1.6%), including 3 participants with anaphylaxis.[33]

Table 1 Overall summary of treatment-emergent adverse events (TEAEs, related or not) in the integrated safety population

	Initial dose escalation (N=944)	**Up-dosing (N=919)**	**300 mg/day (any weeks) (N=770)**	**Overall (any dose) (N=944)**
Participants with ≥1 TEAE (by maximum severity)	481 (51.0%)	891 (97.0%)	687 (89.2%)	933 (98.8%)
Mild	426 (45.1%)	438 (47.7%)	446 (57.9%)	373 (39.5%)
Moderate	54 (5.7%)	430 (46.8%)	226 (29.4%)	522 (55.3%)
Severe	1 (0.1%)	22 (2.4%)	15 (1.9%)	37 (3.9%)
Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Death	0	0	0	0
Participants with TRAEs	426 (45.1%)	788 (85.7%)	444 (57.7%)	851 (90.1%)
Participants with ≥1 serious TEAE	0	7 (0.8%)	8 (1.0%)	14 (1.5%)
Mild	0	2 (0.2%)	0	1 (0.1%)
Moderate	0	3 (0.3%)	4 (0.5%)	7 (0.7%)
Severe	0	1 (0.1%)	4 (0.5%)	5 (0.5%)
Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Death	0	0	0	0
Withdrawal from trial due to AEs*	20 (2.1%)	80 (8.7%)	9 (1.2%)	108 (11.4%)
Participants with ≥1 anaphylactic reaction	6 (0.6%)	80 (8.7%)	76 (9.9%)	143 (15.1%)

AE: adverse event; TEAE/TRAE: treatment-emergent/related adverse event.
*Overall, 3 participants discontinued Palforzia due to anaphylaxis (severe anaphylactic reaction)
15 December, 2018 data cutoff for ARC004 and ARC011 trials
Source: Palforzia EPAR[33]



a Actual time of updosing was variable across trials
Initial dose escalation was not included due to the very short duration (2 days) and intensive in-clinic visit.
31 July, 2020 data cutoff for ARC008 trial, all other trials final.
Source: Casale et al. AAAAI 2021

Figure 5 Proportion of participants reporting any treatment-related adverse event by maximum severity (integrated safety population) [reproduced from Figure 22, Document B of the CS]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company's systematic literature review aimed to identify relevant randomised controlled trials (RCTs). The ERG agrees with this approach. Four RCTs (ARC001, ARC003 [PALISADE], ARC007 [RAMSES] and ARC010 [ARTEMIS]) were identified, all part of the Palforzia clinical trial programme and defined as being randomised double-blind placebo-controlled studies comparing Palforzia with placebo (Figure 7, Document B of the CS). Participants in each RCT also contributed to additional extension studies. A comparison of these studies is provided below (Table 11).

Table 11 Summary of four identified RCTs (Palforzia versus control)

	ARC001	**ARC003 (PALISADE)**	**ARC007 (RAMSES)**	**ARC010 (ARTEMIS)**
Phase	**Phase 2**	**Phase 3**	**Phase 3**	**Phase 3**
Extension studies	ARC002, ARC008	ARC004, ARC008	ARC011, ARC008	ARC008
Participants (treatment/ placebo)	29/26	416/139	506 in total	132/43
Age range	4-21 (26 in Figure 7)	4-55 (4-17 used in economic modelling)	4-17	4-17
Efficacy data available?	Yes	Yes	No	Yes
Safety data available?	Yes	Yes	Yes	Yes
Included in economic modelling?	No	Yes (PALISADE included plus cohorts 1 and 3A of extension study ARC004)	No	Yes (included as sensitivity analysis)

The RAMSES study (ARC007) was not used in the efficacy analyses because this study only assessed safety and tolerability. The ERG was unable to confirm this as no individual references for RAMSES were located, except where the results were

combined with those from other studies. Safety data for RAMSES and its extension study (ARC011) were included in safety analyses reported in Section 2.10.3 (pages 98-99) of the CS; however, these data were not reported separately but pooled with data from PALISADE, ARTEMIS and ARC004. Data from RAMSES were not used in the economic modelling.

The ARC001 study was excluded by the company because it was a Phase 2 trial, relatively small (55 randomised participants in total; 29 participants in the Palforzia arm) and conducted only in the United States.[36] The ERG is not convinced that these are valid reasons for excluding this study. In terms of safety data, participants from ARC001 also contributed to the ongoing extension study ARC008, data from which were used in Figure 22 (page 99) of the CS which describes TRAEs over time. Data from ARC001 or ARC008 do not appear to be used elsewhere in the CS.

The ARC003 study (PALISADE) was the main RCT included in the economic modelling. Although PALISADE randomised participants between 4 and 55 years, only those aged between 4 and 17 (90% of those randomised) were used in the modelling. The ERG notes that using data from a subgroup of all participants loses benefits of the randomised design but agrees with the rationale to restrict analyses to children in the modelling.

ARC004, the extension study of PALISADE, is also used extensively in the company's analyses. Allocation to cohorts was by date, but there was randomisation between the three Cohorts 3A, 3B and 3C. The company included data from two selected cohorts of patients (Cohorts 1 and 3A) who had received daily dosing of Palforzia in PALISADE.

ARC010 (ARTEMIS) is a further RCT, which was used in the company's analyses, although mainly as a sensitivity analysis. The ERG agrees that this study is eligible for inclusion.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

An expected approach would be to conduct a meta-analysis of the eligible RCTs to compare Palforzia and control. This would provide summary effect sizes such as odds ratios that could be used in the cost-effectiveness modelling. However, the company did not conduct any formal meta-analyses and it would not be possible to include such effect sizes without making major changes to the model. Such a meta-analysis would certainly be possible for many outcomes, including for the primary outcome (the proportion of participants tolerating at least 1000mg). Even if the results of the meta-analysis were not used in the economic modelling, it might provide information about the size and precision of the effects of Palforzia and confidence that the data used in the modelling were unlikely to be affected by selection and other biases.

The company also confirmed that they attempted to conduct a network meta-analysis (NMA) including additional comparators (Palforzia, Viaskin-Peanut, oral immunotherapy and sublingual immunotherapy), but a robust analysis could not be conducted due to heterogeneity in the trials' methodology, inclusion criteria and endpoints [company's response to Clarification Question A4]. The ERG is unable to confirm this as no further details were provided.

The alternative approach used by the company was to use individual participant data (IPD) in the economic modelling. The ERG agrees that this approach is reasonable because they have access to the IPD from all available trials. However, the ERG is of the opinion that pooling of data or use of IPD from all eligible randomised studies is the best way to limit the risk of selection bias. The company chose to use PALISADE (ARC003) as the main study in their cost-effectiveness modelling. Data from ARTEMIS (ARC010) were then used as a sensitivity analysis, but data from ARC001 were not used. Pooled data from PALISADE and ARTEMIS were not used because of the differences in study design, in particular the length of the maintenance period (approximately 24-28 weeks in PALISADE; 12 weeks in ARTEMIS). The ERG is of the opinion that pooling data from PALISADE, ARTEMIS and the Phase 2 ARC001 would have been possible but accepts that all these studies show consistent results and agrees with the company that study design

varied across trials and that the addition of the Phase 2 ARC001 to the main Phase 3 trials would not add greater insight about the efficacy of Palforzia.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None

3.6 Conclusions of the clinical effectiveness section

Inclusion of all eligible data from existing trials would lead to greater confidence in the results obtained. However, the ERG recognises that the company has used the ARTEMIS study in a sensitivity analysis, which yields similar results. The ERG is of the opinion that exclusion of ARC001 because of the small sample size is not justified but agrees with the company that its addition would not affect the results and conclusions of the included Phase 3 trials.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review, with broad search terms, to identify any studies evaluating the cost-effectiveness of treatments for peanut allergy in children (aged 4-17). Full details of the systematic review methodology, inclusion / exclusion criteria, search strategy, results, and quality assessment of included studies are provided in Appendix G of the company submission (CS).

The search was not limited by language or date restrictions and searches were conducted up to January 2021. Non-English language articles were excluded during abstract selection. The ERG is satisfied that the database (MEDLINE, EMBASE, CEA registry and HTA database) search strategies provided in Tables 21-24 of Appendix G of the CS, supplemented with grey literature searching are sufficient to identify any existing economic evaluations in peanut allergy.

Fifteen studies evaluating the cost-effectiveness of peanut therapies were identified, data extracted, summarized and quality assessed using the Drummond and Jefferson checklist.[37] None of the 15 identified cost-effectiveness studies were conducted in the UK. The review identified two articles which the ERG considers to be relevant. Both articles relate to an ICER-US assessment of the cost-effectiveness of Palforzia (AR101) or Viaskin plus avoidance compared to avoidance alone.[38] The ERG noted some data extraction errors for the ICER report (ICER, 2019) in Table 28, appendix G of the CS, the data are correctly extracted under Tice et al, and are correctly reported in the CS.[39] The ICER review base case ICER was $88,000 per QALY gained, compared with an ICER of $216,000 for Viaskin. Whilst the results of ICER-US evaluation are not directly transferable to a UK decision making context, the ERG considers the model structure and treatment pathway assumptions from the ICER evaluation to be relevant to the current assessment. Where relevant, the ERG discusses key differences between the ICER model and company submission throughout the report.

Three additional studies that evaluated peanut OITs other than Palforzia, from a US perspective were identified, with substantial variation across the studies in terms of the base case ICE. The ERG is satisfied that these studies, whilst useful in terms of model structure, are of limited relevance to UK decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

The ERG's assessment of the submission against the NICE reference case is provided in Table 12 below.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Yes.** The base case model health states include both patient HSUVs and carer disutility up to patient age 18 obtained from a *de novo* utility study.
Perspective on costs	NHS and PSS	**Yes**, NHS and PSS costs incorporated.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Yes**
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	**Yes**, though substantial uncertainty regarding longer term extrapolations of treatment discontinuation and benefit.

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	**No**. Clinical effectiveness parameters obtained directly from the PALISADE trial for the base case analysis, with sensitivity analyses exploring the use of data from ARTEMIS. Formal evidence synthesis or pooling of effectiveness data (maximum tolerated peanut dose) across studies was not provided.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Partly.** There are no mortality gains in the model. Health effects measured in QALYs, with HRQoL obtained from responses to EQ-5D-Y and EQ-5D-5L questionnaires for current health today (assumed equal to MTD: <300mg state) and three descriptions of model health states (up-dosing, maintenance and MTD: 2000mg, i.e., 6-8 peanuts). Disutilities for accidental exposure and TRAEs were based on a study that used the TTO / SG technique, to estimate utilities for moderate and severe allergic reactions to food.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**No.** Patient HSUVs measured using a pooled data analysis including adolescents with experience of peanut allergy self-report (N=38) and parents / guardians of children and adolescents

Element of health technology assessment	Reference case	ERG comment on company's submission
		with a diagnosed peanut allergy proxy report (N=119). Disutilities for accidental exposure and TRAEs were based on parent / guardian proxy valuations of moderate and severe allergic reaction to food.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Mostly**. Patient HSUVs and carer disutility based on UK national general population tariffs.[40, 41] Disutilities for accidental exposure and TRAEs were based on a study completed by a sample of respondents in Indianapolis, USA.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes.**
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	**Yes.**
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes**, but ERG notes the discount rate was not varied in sensitivity analyses.
EQ-5D, standardised instrument for use as a measure of health outcome; ERG, Evidence review group; HSUV, health state utility values; MTD, maximum tolerated dose, PSS, personal social		

Element of health technology assessment	Reference case	ERG comment on company's submission
services; QALYs, quality-adjusted life years; SG, standard gamble; SHELF, the Sheffield elicitation framework; TRAE, treatment related adverse events; TTO, time-trade off		

4.2.2 Model structure

The company has submitted a Markov cohort state transition model developed in Microsoft® Excel to determine the cost-effectiveness of Palforzia + avoidance compared to avoidance alone for the treatment of children and adolescents with peanut allergy. The model captures the cost and health-related quality of life (HRQoL) implications of treatment up-dosing and maintenance, peanut de-sensitisation, and the potential for longer-term inclusion of peanuts in diet for patients treated with Palforzia. There are five distinct model phases: Initial dose escalation, up-dosing, maintenance, extension, and extrapolation. Separate model structures are used for Palforzia and avoidance arms, as illustrated in Figures 6 and 7, respectively.

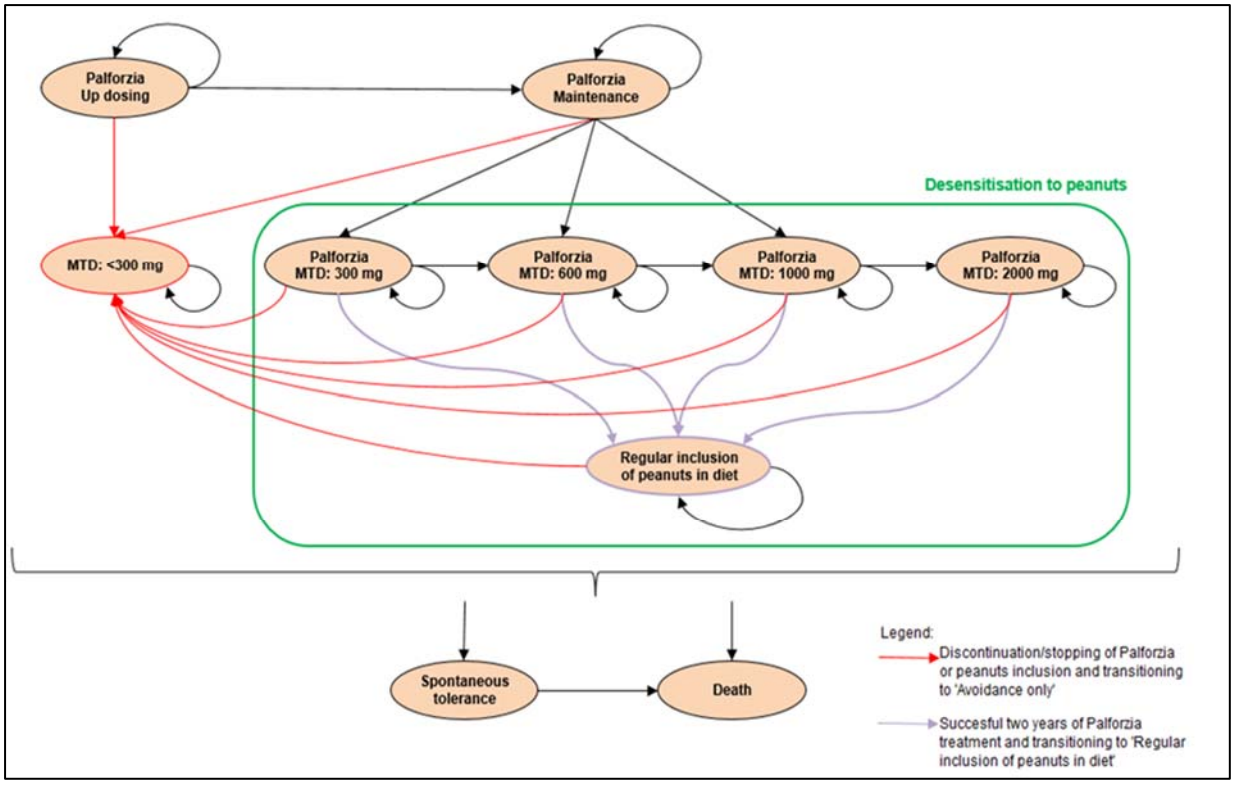


Figure 6. Palforzia arm model structure [reproduced from Figure 24, Document B of the CS)

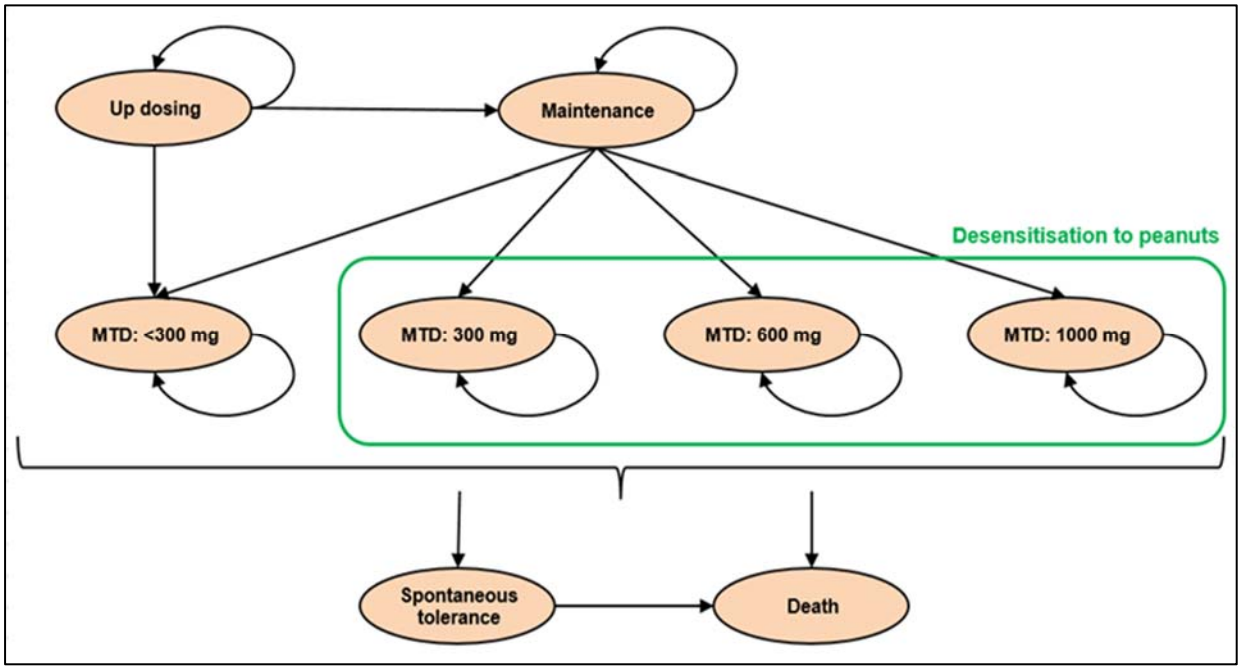


Figure 7. Avoidance arm model structure [reproduced from Figure 25, Document B of the CS)

Treatment up-dosing and maintenance

The model is built around the structure of the PALISADE study, with the cohort in both arms of the model entering in the up-dosing state (max duration: 20 cycles of 14 days) until a maximum maintenance dose of 300mg is achieved, before transitioning into the treatment maintenance state (max duration: 8 cycles of 28 days).

The ERG does not consider it appropriate to include up-dosing and maintenance health states in the avoidance arm of the model. Whilst the model does not include the treatment costs in the avoidance arm it does include the utility implications. The ERG appreciates that the structure may reflect the utility implications of receiving a placebo in the PALISADE study but is concerned that this approach does not reflect routine clinical practice, where patients allocated to a treatment strategy of avoidance should enter the model in the "MTD: <300mg state" (i.e., current health state from the company's utility study). The ERG would have ideally preferred that the up-dosing and maintenance states be removed from the model for the avoidance arm but would also consider an analysis where the utilities in the up-dosing and maintenance states of the Palforzia arm are set equal to the MTD: <300mg state to be appropriate. The magnitude and direction of any biases (for or against Palforzia) associated with this model amendment will depend on the preferred patient and carer utilities for the model (see Section 4.2.7).

Peanut desensitisation

After the treatment maintenance phase, the cohort is assigned to different maximum tolerated doses (MTD) of peanut (MTD: <300mg, 300mg, 600mg, 1000mg), based on results of an exit food challenge at the end of the PALISADE study.

At clarification stage, the ERG queried the appropriateness of having multiple tolerance health states in the model on the grounds that they reduced the sample available to inform transition probabilities, especially in the extension cycle of the model. The ERG asked the company to consider a combined "tolerance" state, where cost and utility parameters were equalised across the tolerance levels in line with the approach taken for the ICER evaluation. The company provided further justification for their approach (company response to clarification point B1) and pointed to evidence from their safety study which showed a reduction in TRAEs and accidental exposures associated with prolonged treatment and higher tolerance

levels. The ERG considers the company's arguments to be valid and therefore accepts that splitting the tolerance states may produce quality of life gains that have better face validity (for example allowing diminishing marginal utility gains with increasing levels of tolerance). The ERG is also aware that the decision to split or combine the tolerance states has only a minimal impact on the ICER.

Patients who have not achieved an MTD of at least 300mg are assumed to discontinue Palforzia treatment at this point and transition to the semi-absorbing "MTD: <300mg" avoidance state where they remain unless they achieve a spontaneous tolerance or die. Patients with an MTD>300mg remain on treatment for a further single extension cycle of the model with a duration 224.5 days taking the cohort up to the point of another food challenge conducted at the end of the ARC004 single arm (Palforzia) extension of the PALISADE study. The proportion of the Palforzia cohort still on treatment at this point is re-distributed again between the four MTD states, with the additional potential of transitioning into a new "MTD: 2000mg" state based on additional measurement from the ARC004 study. As the ARC004 study includes only Palforzia treated patients, it is assumed that the avoidance cohort remain in the MTD assigned at the end of the PALISADE study for the extension cycle of the model.

The ERG is concerned that the exclusion of the MTD: 2000mg state from the extension cycle of the model in the avoidance arm may place an unfair restriction on the avoidance arm by preventing the possibility for patients on avoidance to achieve a tolerance to 6-8 peanuts (MTD: 2000mg). The proportion achieving this is on avoidance is unknown, given that the outcome was not measured in PALISADE, however the ERG appreciates the proportion is likely to be small and any impact on cost-effectiveness would be minimal.

The ERG considers the timing and number of food challenges that would be conducted in clinical practice to be an important area of uncertainty. The company's model assumes that MTD state occupancy is based on the results of two food challenges, one conducted at the end of PALISADE and the other at the end of the ARC004 follow-on study. However, in line with the company response to clarification, the ERG's clinical expert is of the view that one single food challenge would be

conducted in clinical practice for Palforzia (around 2 years) and none for avoidance. It is therefore unclear to the ERG how decisions to discontinue treatment (for MTD: <300mg) could be implemented, or how the realisation of utility benefits could be achieved prior to a food challenge being conducted. The cost and utility implications of this are discussed in Sections 4.2.6 and 4.2.7 respectively.

Long term extrapolation

At the end of the extension cycle (i.e., 2 years), the Palforzia cohort can remain on treatment or discontinue. Those who remain on treatment are assumed to remain in the MTD state achieved in the exit food challenge at the end of the ARC004 study. The cohort may discontinue treatment, transitioning to regular inclusion of peanut in diet, where they no longer incur treatment costs and are assumed to improve their tolerance to a MTD: 2000mg, regardless of the MTD achieved at the exit food challenge from the ARC004 study. A proportion of those who include peanut in diet will revert to a strategy of avoidance where they remain for the duration of the model time horizon, unless they achieve a spontaneous tolerance or die. It is assumed that those who lose a response will not restart Palforzia treatment, even if treatment had previously been successful.

In contrast, the proportion of the cohort in the avoidance arm with tolerance levels over 300mg remain in these designated tolerance states, as per the placebo arm of the PALISADE study, for the duration of the model time horizon, unless they lose their response and transition to the MTD: <300mg state. Both arms of the model are assumed to incur the same chance of developing a spontaneous tolerance or of dying according to the probability of general population age and sex specific all-cause mortality.

Overall, the ERG is generally satisfied that the company's model structure is reasonable reflection of the care pathway for peanut allergy. However, the ERG does have some concerns about the assumptions governing the transition of the cohort through the model health states (addressed in Section 4.2.6). In particular, the ERG notes that the combination of probabilities that govern long-term occupancy in the "peanuts in diet" health state (i.e., transitions into the state, and adherence to inclusion of peanut in diet) are important drivers of cost-effectiveness as they

determine the proportion of Palforzia treated patients who can achieve the benefits of treatment without incurring any long-term treatment acquisition costs.

4.2.3 Population

The model was run for a cohort of children and adolescents with a confirmed peanut allergy diagnosis. The model starting age is 10, reflecting the mean age in the PALISADE (ARC003) trial for the subgroup (499/555 =89.9%) of participants aged 4-17 at baseline. The ERG's clinical expert confirms that the characteristics of the modelled cohort (and trial population) are similar to those that would be deemed eligible for treatment with Palforzia in UK clinical practice. The ERG is satisfied that the modelled population reflects the characteristics of the participants in the age 4-17 subgroup of the PALISADE study, is consistent with the licensed indication for Palforzia, and the decision problem for this assessment.

4.2.4 Interventions and comparators

Intervention

The intervention is Palforzia (AR101), Aimmune Therapeutics, a Nestle Health Science Company, an oral immunotherapy indicated for the treatment of peanut allergy in children and adolescents (aged 4-17). The intervention is administered in three phases (initial dose escalation over a single day from 0.5mg to 6mg, up-dosing through 11 dose increments (3mg, 6mg, 12mg, 20mg, 40mg, 80mg, 120mg, 160mg, 200mg, 240mg and 300mg) and maintenance therapy with a daily dose of 300mg. Initial escalation and the first dose of each up-dosing level should be administered in a healthcare setting to monitor for risks of severe allergic reaction. The intervention should be used in combination with a peanut-avoidance diet. Further details are provided in the full UK SmPC and EPAR report included in Appendix C of the CS document.

The ERG is satisfied that the intervention (Palforzia + avoidance, hereafter referred to as "Palforzia") is modelled in line with the scope for this appraisal and in line with the licensed authorisation for up to two years of treatment. However, the ERG notes that, due to a lack of efficacy data, the SmPC were unable to make a recommendation about treatment beyond two years.

Comparators

The comparator in the company's economic model is a strategy of strict avoidance only.

Whilst other unlicensed comparators, such as OITs and SLITs and Viaskin-Peanut exist and have been studied in clinical trials, they are not licensed for treatment of peanut allergy in the UK and are therefore not appropriate as comparators. Whilst some patients may attempt to achieve peanut desensitisation through inclusion of small amounts of peanut in diet, the ERGs clinical expert considers the compactor for the assessment to be reasonable and reflective of how many patients are managed in routine clinical practice.

4.2.5 Perspective, time horizon and discounting

An NHS and personal social services (PSS) perspective was adopted for the costs. Whilst the economic model includes the functionality to also include societal costs, these have not been included for the current assessment. The ERG is therefore satisfied that the costing perspective is in line with the NICE reference case.[42]
The model time horizon was for 90 years, up to a maximum age of 100. The company provide scenario analyses with shorter time horizons of 5 and 20 years.

The ERG considers the lifetime horizon to be generally appropriate for the base case analysis but notes that shorter time horizons may mitigate some of the uncertainties associated with the assumption that a substantial proportion of the cohort can discontinue treatment, whilst maintaining the benefits of treatment (through inclusion of peanut in diet) over a full lifetime.

Costs and QALYs were discounted by 3.5% per annum in the model, which is consistent with the NICE reference case.

The discount rates applied in the base case analysis are appropriate and the ERG is satisfied that discounting has been correctly applied in the model. However, the company have not provided any sensitivity analysis around this source of methodological uncertainty. The ERG therefore varies the annual discount rate between 0% and 6% for costs and QALYs in scenario analyses.

4.2.6 Treatment effectiveness and extrapolation

The company model utilises treatment specific transition probabilities to govern the flow of the cohort between the health states in each arm of the model over five distinct phases: Initial up-dosing (cycle length 1 day), up-dosing (cycle length 14 days), maintenance (cycle length 28 days), extension (cycle length 225.5 days), and extrapolation (cycle length one year). In the base case the duration of these phases is aligned with observed durations from PALISADE and its extension ARC004. Details of the transitions allowed in the model are provided in Section 3.2.9 of the CS. The cycle length of the model varies by phase as indicated above and detailed in Table 29 of the CS. Data to inform the transition probabilities were from

PALISADE and ARC004 in the base case, and a scenario using data from ARTEMIS in combination with ARC004 was also provided.

Derivation of transition probabilities

From initial dose escalation (cycle length one day), patients either discontinue treatment and transition to 'Tolerated dose of peanut protein <300mg' or continue in the 'Up-dosing' health state. The discontinuation probability following initial dose escalation ([redacted]) comes from PALISADE individual patient level data.

For those who remain in the 'Up-dosing' state of the model, time dependent transition matrices determine the cycle specific probability of discontinuing treatment and reverting to 'Tolerated dose of peanut protein <300mg', continuing in the 'Up-dosing' state, or transitioning to the 'Treatment maintenance' state. Transitions during this phase of the model also come from PALISADE individual patient level data.

Patients who enter the 'Treatment maintenance' state before the end of the up-dosing phase of the model either remain there or discontinue treatment and transition to the 'Tolerated dose of peanut protein <300mg'. From cycle 22, marking the beginning of the maintenance phase of the model, patients can transition to the desensitised to peanut states (tolerated dose 300mg, 600mg or 1000mg), where they are held until the end of the maintenance phase. By cycle 30, the beginning of the extension phase of the model, all patients have transitioned out of the 'Treatment maintenance' state and are distributed between the 'Tolerated dose' states (<300mg, 300mg, 600mg, 1000mg). The beginning of cycle 30 represents 72 weeks from initiation of treatment, which aligns with the completion of PALISADE. The company show how the state distribution in the model at this timepoint closely matches the observed state distribution at PALISADE exit in both the Palforzia and SoC arms.

A single cycle (cycle 30) is used to represent the extension phase of the model, with the transition probabilities informed by the transitions observed in Cohorts 1 and 3A during the ARC004 study (open label extension of PALISADE). Table 32 of the CS provides the count data underpinning the transition probabilities applied in the model. Transitions between the maximally tolerated dose states only apply to those in the

Palforzia arm of the model during the extension cycle and include transitions to a higher level of tolerance ('Tolerated dose 2000mg'); Those in the avoidance only arm are held in their current state as no data are available for avoidance patients in ARC004. The cycle length for the model extension phase (225.5 days) takes the time horizon out to two years post-treatment initiation, which aligns with the observed follow-up duration for ARC004 from PALISADE baseline.

The ERG generally accepts the company's approach to estimating transition probabilities during the phases of the model that correspond to the observed follow-up periods of PALISADE and its extension (ARC004). One potential issue is that since tolerance to 2000mg of peanut protein was assessed only in ARC004, this state can only be entered in the Palforzia arm of the model. We cannot rule out the possibility that the MTD state distribution might also have improved further for the few patients who achieved tolerance of ≥ 300mg in the placebo arm of PALISADE had they also been followed-up at two years. However, this would only potentially apply to a very small number of patients. The ERG is therefore satisfied that any biases would be small in magnitude and would be unlikely to have a substantial impact on cost-effectiveness.

From cycle 31, the model enters the extrapolation phase, and the tolerated dose is carried forwards from this point onwards unless patients discontinue treatment (assumed to transition to 'Tolerated dose <300mg'), or transition to the 'Spontaneous tolerance', 'Regular inclusion of peanut in diet', or 'Dead' state. The chance of spontaneous tolerance is set to 5% over the time horizon of the model based on expert opinion elicited by the company and does not differ by treatment arm or health state. Death is modelled based on UK life tables, and again the probability does not vary by treatment or health state.

For patients who continue Palforzia treatment to two years, the company conducted a SHELF expert elicitation exercise to inform the ongoing treatment duration beyond two years. The experts advised that most patients in the UK would likely switch to regular inclusion of peanut in their diet after [redacted] years instead of continuing with Palforzia treatment. Using the expert elicitation methods described in Appendix N of their submission, the company suggest that [redacted] will remain on Palforzia treatment and maintain their tolerated dose health state after [redacted] years, whilst [redacted] will transition to

regular inclusion of peanut in their diet after [redacted] years. Of the [redacted] who switch, they use the SHELF expert elicitation methods to support the assumption that [redacted] will subsequently stop and revert to avoidance ('Tolerated dose <300mg) over the course of [redacted] years (see Table 48 of the CS).

The ERG accepts the likelihood that patients who achieve tolerance at [redacted] years will be encouraged to switch to regular inclusion of peanut in their diet. However, without data on the long-term use of Palforzia in routine NHS practice, the proportions and timings are uncertain. The company used a recognised methodology for eliciting expert responses, but the ERG notes some uncertainties related to the process. In particular, the percentage stopping treatment following switching to regular inclusion of peanut in their diet was elicited [redacted] *(Appendix N, Figure 5, Company submission). It is not clear how* [redacted]*, and how the* [redacted] *was derived. This is of some importance,* [redacted] *Further, the model assumes no further discontinuation beyond* [redacted] *years after switching to regular inclusion of peanut in diet. There may be potential for further drop out beyond* [redacted] *years, particularly* [redacted]*. Another issue relates to the fact that* [redacted] *(Company submission, Appendix N, Figure 2).*

The ERG has some further concerns regarding the implications of applying the switch to regular inclusion of peanut in the diet as a flat percentage across the maximum tolerated dose (MTD) states (300mg, 600mg, 100mg and 200mg) at two years. Since health state utility is set equal in the model for the 'Tolerated dose of

peanut 2000mg' and 'Regular inclusion of peanut in diet' state, and lower for those who achieve lower levels of tolerance on Palforzia (see below), this infers that switching results in an immediate increase in the level of tolerance (to 2000mg or 6-8 peanuts) for those who do so from the MTD states of 300mg, 600mg and 1000mg. Whilst plausible that patients will continue to improve their tolerance with regular inclusion of peanut in the diet, there is some uncertainty associated with this assumption that would benefit from sensitivity analysis.

Reactions to accidental exposure to peanut protein

Reactions to accidental exposures requiring treatment are considered as another efficacy outcome in the model. Their frequency/probability in the up-dosing and maintenance phase is informed by observed data from PALISADE. The proportion of all treated reactions (over the up-dosing and maintenance phase combined) that required treatment with adrenaline was applied to reactions in the up-dosing and maintenance phase (see Table 33 of the CS). No reactions in the Palforzia arm required treatment with adrenaline (0/24) while 23% (3/13) in the placebo arm did.

The ERG is generally satisfied with the company approach of basing reactions during the up-dosing and maintenance phase on PALISADE data but note the small numbers of events. This is most pertinent to the number of observations on which to base the breakdown of those requiring treatment with adrenaline.

Beyond year one, the company use a separate risk reduction model using baseline and follow-up data from the PALISADE trial rather than relying on the observed data from ARC004, noting the low patient numbers and rarity of the events as justification.[43] The intuition of the approach, as the ERG understands it, is as follows:

1. The lifetime number of systemic allergic reactions (SAR) to peanut protein and participant time at risk (participant age in days) were collected for each participant in PALISADE at baseline
2. The baseline MTD of peanut protein was established for each participant from the PALISADE baseline DBPCFC, and the minimum eliciting dose (MED) for a SAR (prior to treatment) was assumed to be one dose higher than the MTD.
3. Participant level data on the number of SARs, time at risk (in days), and the MED are used to estimate (by maximum likelihood) the distribution of daily

accidental peanut exposure (mg), assuming either a Weibull, lognormal or loglogistic form, and maximum value of 1500mg.

4. The baseline daily risk of a SAR is assessed as the probability that the estimated daily accidental peanut exposure distribution is greater or equal to the MED, and then converted to an annual risk.
5. The MED at follow-up is established from the exit DBPCFC of PALISADE and used to calculate the post-treatment MED (following the same approach as 2.) Note, because 1000mg was the highest dose assessed in the PALISADE DBPCFC, the MED for those with a MTD of 1000mg was conservatively assumed to be 1000mg.
6. The post-treatment daily and annual risk of a SAR was determined using the post-treatment MED and the approach described in 4.
7. The relative risk reduction was calculated by comparing the post-treatment annual risk to the baseline annual risk of a SAR and presented overall and by the MTD achieved (300mg, 600mg/1000mg).

The company indicate that they chose the lognormal distribution for daily peanut exposure, which gave the middle ground estimate for annual baseline risk ([redacted]) (See Table 35 of the CS). Based on this model, the relative risk reduction was estimated to be [redacted] and [redacted] for those achieving a MTD of 300mg and 600mg/1000mg respectively. Since the 2000mg dose was not assessed in the PALISADE DBPCFC, a MTD of 2000mg was also assumed to confer a [redacted] relative risk reduction, as was regular inclusion of peanut in the diet. The company further disaggregate the SARs into those requiring treatment with adrenaline and those not, based on the observed frequencies in PALISADE.

The ERG follows the logic and assumptions of the company's approach, and believe it seems reasonable. Limitations include the assumption that the daily accidental exposure distribution (as derived at baseline) is constant over time. If the exposure distribution decreases or increases over time, the approach could give biased estimates of the risks and or risk reductions by tolerance level. For example, if those treated with Palforzia take less care about avoidance than they otherwise would and increase their daily exposure distribution relative to avoidance only, the full risk reduction associated with improved tolerance may not be realised. Conversely,

patients may get better at practicing avoidance over time, and reduce their daily exposure distribution, lowering the risk of events for both avoidance and those who improve their tolerance with Palforzia. Given the uncertainty in the approach, the ERG asked the company to provide a scenario using data from ARC004 to estimate the risk of events for all those who develop tolerance ≥300mg. Given the very small numbers available to inform event rates for these Palforzia treated individuals, a single event rate was calculated for the tolerance dose states combined. Whilst this analysis (provided in response to clarification question B6) appeared to suggest little difference in the risk of reactions due to accidental exposure in those with tolerance <300mg compared to those with any tolerance ≥300mg, the impact on the ICER was low, suggesting it is not a key driver of cost-effectiveness.

Treatment related adverse events

In addition to reactions due to accidental exposure, the model captures treatment related adverse events for those on Palforzia, including anaphylactic reactions. These were informed separately by model phase, considering evidence suggesting that the frequency of adverse events and their severity decreases the longer patients stay on Palforzia.[34]

Treatment related anaphylactic reactions

The company noted the rarity of severe treatment related anaphylactic reactions, and so argued to exclude these from the model and include only mild or moderate reactions. The number and per cycle probability of mild and moderate treatment related anaphylactic reactions during Palforzia up-dosing and maintenance were taken from the PALISADE trial (see tables 38 and 39 of the CS). To ascertain the probability of treatment related adverse reactions by the maximum tolerated dose states, data from Cohorts 1 and 3A of the ARC004 study were applied (see tables 40 and 41 of the CS). Numbers of events were low, and none were observed in the tolerated dose of peanut protein 300mg state. Therefore, it was assumed that the rate in this state would be the same as that observed in the up-dosing and maintenance phase of the PALISADE study combined. As no observations were available to inform the event rate for the tolerated dose of 2000mg or regular inclusion of peanut in diet, this was assumed equal to that of the 1000mg health state.

The ERG is satisfied with the company's implementation of their stated approach, but again note the very small numbers of events available to inform the rates, particularly during the extension and extrapolation phases based on ARC004 data. It is possible that for the purpose of informing adverse events, the company could have utilised pooled data from other studies that assessed safety outcomes, including ARTEMIS, ARC001 and its extension ARC002. However, this may not have overcome the problem of the limited data available to inform the extension and extrapolation phases of the model as there was no extension data available for ARTEMIS and ARC002 included only a small number of participants. The ERG also questioned the company's decision to exclude severe treatment related anaphylactic reactions from the model because of their rarity. The ERG preference would have been to include them all and disaggregate them by severity based on the observed proportional distribution. Such an analysis was requested at the clarification stage, which the company provided. Inclusion of these events had minimal impact on the ICER - assuming the same cost and utility impact as reactions to accidental exposure to peanut protein requiring treatment with adrenaline (see company clarification response, question B3).

Other treatment related adverse events

Treatment related non-anaphylactic adverse events were similarly incorporated by treatment phase, based on data from PALISADE for up-dosing and maintenance. For adverse events by tolerance states, the numbers in ARC004 were very low, and so the company argued for their exclusion from the model. The TRAEs were grouped by organ system, and the company noted that only mild serious, moderate and severe treatment related adverse events that occurred in ≥5% of patients in at least one arm of the study population of PALISADE or ARTEMIS (considered as a scenario) were included. The ERG was uncertain whether severity levels within organ systems were considered as separate categories for application of the 5% threshold. Therefore, the ERG asked for a full breakdown of TRAEs by organ system and severity in the clarification letter. The ERG also asked the company for an analysis which include all TRAEs that have significant resource or utility implications, including during the long-term extrapolation using data from ARC004. The company provided both in their response (see company clarification response, question B4).

The ERG is satisfied with the company's clarification and further analysis around the incorporation of TREAs and acknowledges that it has minimal impact on the ICER.

4.2.7 Health related quality of life

As there are no assumed life year benefits in the model, QALY gains are based entirely on differences in quality of life between the Palforzia + avoidance and avoidance only arms of the model. In line with the model structure, QALY gains for Palforzia accrue mainly through the substantial proportion of the cohort who enter the "peanuts in diet" health state in the Palforzia arm compared to none in the avoidance arm, and also the lower proportion of patients in the un-tolerated peanut MTD: <300mg health state over time. Within these health states, QALYs can accrue from increased patient quality of life, reduced carer disutility, additional treatment related adverse events and lower risks of accidental exposure to peanut.

Patient health state utility values (HSUVs)

The company obtained HSUVs from a *de novo* utility study (see appendix P of the CS). The study was conducted with a sample of N=157 respondents, including adolescents [redacted]) between the age of [redacted] with experience of peanut allergy, and N=117 parents/ guardians of children with peanut allergy. Adolescent respondents were asked to self-report their own health using the EQ-5D-Y (assumed to reflect their responses for a MTD <300mg health state), and to provide EQ-5D-Y responses for three additional health states described to mirror three model health states (up-dosing, maintenance, and tolerance level MTD: 2000mg). The parent / guardian respondents were asked to provide proxy responses for the same health states for their own children, who have peanut allergy. EQ-5D-Y responses were then translated into utilities using nationally representative EQ-5D valuation sets in the UK. The company base case analysis pooled HSUVs across a mix of [redacted] as well as across adolescent responses and caregiver proxy responses.

The ERG considers the company's decision to use the EQ-5D-Y to measure quality of life associated with the health state descriptors to be appropriate. Whilst there may be some uncertainty surrounding the transferability of HSUVs obtained from the

EQ-5D-Y in an adolescent population to the same health states in both the adult population (i.e., in cycles after the cohort age turns 18) and for children aged [redacted], the ERG accepts that the company's approach is reasonable.

However, the ERG does not consider it appropriate to use proxy reports from a sample of parents / guardians, [redacted] of whom are not allergic to peanuts themselves, when a sample of treatment naïve adolescents with experience of peanut allergy (N=38) can be used instead. The ERG also notes that the use of self-reported EQ-5D responses from patients is more congruent with the NICE reference case. Furthermore, the ERG is concerned that carer valuations may inadvertently be capturing anxiety and concern to parents, as opposed to isolating the impact on the child / adolescents' quality of life. Given that carer disutility is also included within the model, the ERG is concerned that using parental responses may partially double count the burden on carers. The ERG's preferred sample for obtaining HSUVs is therefore N=38 [redacted] adolescent respondents to the [redacted] survey who have experience of peanut allergy. These data are reported in the *de novo* utility study included in appendix P of the CS.

The valued health states were applied directly to the model, but assumptions were required for the most appropriate HSUVs for states not included in the utility study (peanuts in diet, spontaneous tolerance and the 300mg, 600mg and 1000mg MTD states). The company assume that the HSUV for the "peanut in diet" and "spontaneous tolerance" health states is equal to that of the MTD: 2000mg state. The company assume that the HSUVs for the remaining tolerance health states can be calculated by using a linear interpolation between the maintenance and tolerated (MTD: 2000mg) HSUVs.

The ERG's clinical expert considers the description of the health states (available from appendix P of the CS) to be appropriate and reflective of the descriptions that might be provided to patients in these states in clinical practice. Whilst the assumptions used to infer HSUVs for states not included in the utility study generates some uncertainty, the ERG considers the assumptions to be reasonable given the data available.

Application of HSUVs in the model

The company has applied HSUVs specific to the up-dosing and maintenance states in both model arms.

The ERG accepts that the assumption reflects the use of placebo in the PALISADE study. However, it lacks face validity in clinical practice where patients would not receive a blinded treatment, and therefore could not reasonably incur the utility implications of up-dosing and maintenance. The ERG therefore considers it more appropriate to consider an analysis where the utilities in the up-dosing and maintenance states of the avoidance arm are set equal to the MTD: <300mg state.

Health state occupancy up until the end of the extension cycle is informed by the results of two food challenges, one at the end of the PALISADE trial and one at the end of the ARC004 extension study. However, the company base case incurs the costs of only one food challenge at approximately two years. The base case therefore assumes that the utility implications associated with the MTD state (MTD: <300mg, 300mg, 600mg and 1000mg) at the end of PALISADE can be realised before the results of the two-year food challenge would be known.

The ERG's clinical expert agrees with the point raised by the company in response to clarification queries that one food challenge for Palforzia treated patients is more reflective of UK clinical practice than two. The ERG's clinical expert also considers it appropriate to conduct this food challenge at approximately 2 years after starting treatment (aligned with the follow up ARC004 study). Because the use of food challenges in clinical practice is likely to be less than in the trials, it is unclear to the ERG how the utility gains associated tolerance levels achieved at the end of the PALISADE study applied for the extension cycle of the model would be realised in real-world use of the drug if patients and clinicians are unaware of the MTD. The ERG therefore considers the company's scenario analysis (provided in response to clarification queries) applying maintenance utility up until the time point of the food challenge at two years to be more appropriate.

The company and ERG preferred patient HSUV assumptions are compared in Table 13.

Table 13 Summary of company and ERG preferred patient HSUV data and assumptions

Assumption / data source	Company base case	ERG base case
De novo utility study sample	N=157 [redacted] respondents completing [redacted] with a mix of adolescent self-reported and carer proxy reported EQ-5D-Y profiles for described health states.	N=38 [redacted] adolescent respondents with experience of peanut allergy providing direct EQ-5D-Y responses to the described health states.
HSUVs for model health states included in utility study	HSUVs derived from health states included in the utility survey applied directly to model health states	ERG and company preferences aligned.
HSUVs for health states not included in utility study	MTD: 300mg, 600mg and 1000mg HSUVs calculated using linear interpolation between maintenance and MTD: 2000mg states. Utility values for "peanuts in diet" and "spontaneous tolerance" assumed equal to MTD: 2000mg state.	ERG and company preferences aligned, but ERG notes uncertainty surrounding the most appropriate values for the MTD health states that were not included in the utility study.
HSUVs for up-dosing and maintenance states in the avoidance arm of the model	Elicited utility values from a *de novo* utility study for up-dosing and escalation applied in both model arms to reflect the use of a blinded control in the PALISADE study	Prefers the application of up-dosing and maintenance utilities be removed from the

Assumption / data source	Company base case	ERG base case
		avoidance arm and replaced with HSUVs = MTD:<300mg health state, to reflect that blinded controls would not be used in real-world clinical practice in the avoidance arm.
HSUVs for different MTD states prior to food challenge	Base case allows utility gains to be accrued prior to a single food challenge at 2 years	ERG agrees with a single food challenge at two years but prefers company scenario analysis applying maintenance utility up to the food challenge time point.

Carer disutility

The company base case analysis applies carer disutilities, up to patient age 18, in the up-dosing, maintenance, MTD<300mg, MTD: 300mg, MTD: 600mg and MTD: 1000mg health states in the model. No carer disutility is assumed for the MTD: 2000mg health state, "spontaneous tolerance" health state or "peanut in diet" health state. Carer disutilities for the model are obtained from the same utility study of N=157 respondents were used to derive patient HSUVs. Parents / guardians of children with peanut allergy completed the EQ-5D-5L reporting their own health today (used for the <300mg health state) and the same three additional described health states used to derive patient HSUVs.

The ERG queries the appropriateness of including carer disutility in this assessment and note that the NICE reference case is not particularly clear on this matter. The NICE reference case stipulates that "direct" health effects on carers can be considered, "where relevant". A judgement call is required with regards to what is

considered "direct" health effects and whether concern / worry about an uncertain outcome (anaphylactic reactions, accidental exposure to peanuts) that might occur within a health state, most likely the MTD: <300mg health state could be considered "direct". The second uncertainty is whether it is "appropriate" to consider carer disutility in this population and condition. Carer disutility is often considered in appraisals where there are clear direct implications of health state occupancy for caregivers, such as in Alzheimer's disease, or in multiple sclerosis or stroke where care giving involves additional direct care for patients well beyond what would be required for a similar health individual without the condition. However, parental / guardian disutilities are also considered in appraisals of conditions in paediatric populations. The ERG also appreciates that there is likely to be substantial additional concern among parents / guardians about the risk of accidental exposure that could be alleviated with effective treatment. Whilst there is substantial uncertainty, on balance, the ERG considers the inclusion of carer disutility to be reasonable.

The ERG considers it appropriate not to apply carer disutility in the MTD: 2000, peanuts in diet or spontaneous tolerance states, where accidental exposure is highly unlikely and also agrees with the decision not to apply carer disutility beyond patient age 18. Whilst there may be some uncertainties associated with pooling data for parents / guardians of [redacted], as well as pooling [redacted] the ERG does not have the same concerns as for the patient HSUVs and therefore considers the company's use of the full sample to estimate carer disutility to be reasonable.

The company has assumed an average of [redacted] carers, based on the weighted average number of respondents stating 1, 2 and 3+ (assumes 3 for calculation purposes) carers respectively in the pooled sample.

The ERG considers the number of carers to be an area of additional uncertainty that would benefit from discussion and further sensitivity analysis.

Disutility associated with accidental exposure to peanuts and treatment related adverse events

The company base case model assumes a further disutility to patients associated with either moderate (assumed duration 1 day, no adrenaline required) or severe (assumed duration 2 days, adrenaline required) allergic reaction due to accidental peanut exposure. The disutilities for the experience of each state were -0.07 (moderate) and -0.09 (severe), sourced from a study of disutilities across several paediatric conditions.[44] Disutilities were obtained using parental proxy of children's EQ-5D responses for health states describing moderate and severe food related allergic reactions. Valuations were provided using both the standard gamble and time-trade-off method, both of which generated the same results for allergic reaction states. The survey was completed by a sample of respondents in Indianapolis, USA.

The company has not provided any details or justification as to why they have chosen the Carrol and Downs study as the basis of their disutility data, or if other potential data sources exist that could have been used instead.[44] It is questionable whether the valuations provided by a US sample are reflective of the preferences of the UK general population.The ERG would have preferred if utilities were based on responses to the EQ-5D and valued using a nationally representative sample of the UK general population. The direction of any bias is unclear, but the ERG is satisfied that it is likely small in magnitude due to the assumed short duration of allergic reaction events. The assigned utilities are therefore not a major driver of cost-effectiveness results.

Table 14 summarises the company base case and ERG preferred utilities.

Table 14 Summary of company base case and ERG preferred utilities for the economic model.

Assumption / parameter	Company base case		ERG preferred	
	Patient HSUV	Carer disutility [A]	Patient HSUV [B]	Carer disutility
Treatment up-dosing (Palforzia)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment up-dosing (avoidance)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment maintenance (Palforzia)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment maintenance (avoidance)	[redacted]	[redacted]	[redacted]	[redacted]
MTD: <300mg	[redacted]	[redacted]	[redacted]	[redacted]
MTD: 300mg	[redacted]	[redacted]	[redacted]	[redacted]
MTD: 600mg	[redacted]	[redacted]	[redacted]	[redacted]
MTD: 1000mg	[redacted]	[redacted]	[redacted]	[redacted]
MTD: 2000mg	[redacted]	[redacted]	[redacted]	[redacted]
Peanuts in diet	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous tolerance	[redacted]	[redacted]	[redacted]	[redacted]
Accidental exposure (mod.)	-0.0002	0.000	-0.0002	0.000
Accidental exposure (severe)	-0.0005	0.000	-0.0005	0.000
Anaphylactic TRAEs	-0.0005	0.000	-0.0005	0.000
All other TRAEs	-0.0002	0.000	-0.0002	0.000
Death	0.000	0.000	0.000	0.000

Abbreviations: A: Avoidance; MTD: Maximum tolerated dose; P: Palforzia

[A] All carer disutilities multiplied by [redacted] in the company economic model to reflect an average of [redacted] carers per patient based on the company's utility study.

[B] HSUVs taken or derived from those reported in the Table 9 of Appendix P to the CS; disutility for accidental exposure and TRAEs as per the company base case.

[C] Utilities for the Palforzia and avoidance arm in these states are different because the interpolation takes place from the maintenance state value in the avoidance arm in the company base case model, but from the MTD: <300mg in the ERG preferred model.

4.2.8 Resources and costs

The company model incorporates drug costs, administration costs, disease management costs, treatment related adverse event costs, and costs of treating reactions to accidental exposure to peanut.

Drug and administration costs

Drug and administration costs for Palforzia are outlined in section 3.5.1 of the CS (Document B). A [redacted] per day, is applied for each dose of Palforzia (range .5-300mg). The cost is adjusted for compliance in the company model using the proportion of prescribed doses in PALISADE taken by patients ([redacted]).

There is no discussion of the potential for wastage in the company model. Depending on the quantity of the drug supplied to patients during the different phases of the model, there is potential for variable levels of wastage among those who discontinue treatment. The potential may be greater in the maintenance and extension phases, where cycle lengths are longer. The ERGs clinical advisor suggested that patients would be supplied with repeat prescriptions from their GP for a 28-day supply at a time, suggesting that those who discontinue treatment during the maintenance, extension or extrapolation phase of the model, might be expected to waste 14 daily doses on average.

A further issue with respect to treatment costs, is the company's assumption that all patients who achieve a maximally tolerated dose of <300mg by the end of maintenance treatment (corresponding to the PALISADE exit DBPCFC) discontinue treatment immediately. The problem with this relates to the company's further assumption that only one food challenge is assumed to take place in the model at two years (corresponding to the food challenge at exit ARC004). Thus, patients and clinicians would not know the true tolerance state until two years, and so would not know to stop treatment earlier due to a lack of response. The ERG queried this in the clarification letter. In response, the company noted that based on clinical advice they expect only one food challenge to take place in clinical practice, and that this may occur anywhere from around the end of year 1 to the end of year 2. However, they did include a scenario in their response that included the cost of two food challenges to reflect the design of the clinical trials. This had only a small impact on the ICER. However, given the feedback from clinicians, it seems unlikely that this scenario

accurately reflects what will happen in clinical practice if Palforzia is approved. Therefore, the ERG believe it is appropriate to explore alternative assumptions around the timing of a single food challenge test. For these scenarios, patients who achieve a tolerated dose of <300mg should not stop incurring treatment costs until the timepoint at which the food challenge is assumed to occur. Similarly, it is of the ERGs belief that patients should not accrue the utility benefit of improved tolerance states until the timepoint at which the food challenge occurs.

With respect to administration, initial dose escalation and the first dose in each new up-dosing level need to be administered in a health care setting capable of managing severe allergic reactions. The initial dose escalation (IDE) is assumed to occur on a single day as a day case admission, and incorporates the resources as outlined in Table 62 of the CS: allergist time for education and administration, nurse time for administration, and nurse time for monitoring. Further clarification and justification for the IDE resource use assumptions were provided by the company in response to the clarification letter.

For subsequent visits for each new level of up-dosing, the NHS reference cost for outpatient attendance (Service 313 'Clinical Immunology and Allergy Service') was applied.[45] Following up-dosing, the cost of administration is assumed to be zero as there is no requirement for dose adjustments.

Based on the clarification response provided, the ERG is satisfied that the expected cost of staff time for IDE is adequately captured in the model. The cost associated with use of facilities is less certain, as use of treatment space may not be captured in the staff cost multipliers applied. That said, some of the staff time requirements do seem to be quite conservative. The outpatient code for subsequent visits appears appropriate. With respect to zero administration costs being applied in the long-term, there may be a small cost associated with the provision of repeat prescriptions, but this is unlikely to have a material impact on the ICER.

Food challenge test

The company base case model assumes the cost of a single food challenge test at 2 years to establish knowledge of tolerance level. This was described as optional in the company's original submission document but was applied universally in the company model. As indicated above, without it, it is unclear how treatment would bring about improved health related quality of life associated with knowledge of improved tolerance levels, and how treatment stopping due to lack of tolerance would be achieved. For the food challenge itself, the cost of £276.34 was applied, inflated from the value of £256 applied in the previous NICE Diagnostic Assessment Review of ImmunoCAP ISAC 112 for multiplex allergen testing.[46]

The specific source of the £256 applied for the oral food challenge in the previous NICE appraisal is not clear from the published document, but the ERG believe it seems reasonable based on clinical advice received.

Routine monitoring and other costs

The company describe a systematic literature review of health care resource use and costs associated with peanut allergy and its management, but most of the identified studies were from a US perspective. Therefore, the company have estimated disease management resource use based on clinical expert opinion, as outline in section 3.5.4 (and Table 64) of the CS. Resources considered included allergist appointments, dietician appointments, pulmonologist appointments, routine paediatrician/GP appointments, prescribed adrenaline, and high dose antihistamine use. Based on clinical expert opinion, resource utilisation associated with disease management was assumed to be the same in both arms of the model, and equal across the health states except of the spontaneous tolerance state. Palforzia treatment is assumed to incur no additional monitoring costs over avoidance only. Costs associated with TRAEs and reactions due to accidental exposure were considered separately.

Based on the ERGs clinical advice, the ERG has no substantive issues with the company's approach to general management/monitoring resource use.

Reactions to accidental exposure to peanut protein

The company approach is outline in section 3.5.5 of the CS. Resource use for reactions that require treatment with and without adrenaline was considered separately (see Table 65 of the CS).

The ERG has a concern regarding the unit cost applied by the company for ambulance use (£496.54). The company describe how this has been derived by adding the average cost per call (£190) and the average cost per attendance (£270) from a previous NHS Ambulance Services report and inflating this to the current cost year using the consumer price index.[47] From the source document, these costs reflect the total expenditure divided by total calls handled, and total expenditure divided by total attendances. Thus, it is not appropriate to add them together. Even the cost per attendance on its own may be high as it includes an allocation of cost for non-attended calls. However, it provides a more appropriate estimate than the addition of the two averages included in the company model. Therefore, the ERG assesses the impact of setting the ambulance attendance cost at £282.25 (£270 inflated to 2018/2019 prices using the health service inflation indices provided by the PSSRU).[48] An alternative and probably more appropriate unit cost is the reference cost for ambulance services (ASS02, See and treat and convey) - £257.[49]

Other unit costs appear appropriate, and the frequencies of resource use appear reasonable based on the ERG clinical expert's opinion.

Treatment related adverse event costs

For treatment related anaphylactic reactions, similar resource use assumptions to those applied for reactions to accidental exposures were applied. However, all were assumed to require adrenaline, but only a proportion were assumed to require ambulance use and A&E attendance. The company assumed that all accidental exposures requiring adrenaline would incur ambulance and A&E costs in line with guidance, and so the ERG queried the reason why the same assumption was not applied for treatment related reactions requiring adrenaline use. The company response (question B9 of the clarification letter) focusses on the predictability of treatment related anaphylactic reactions, and their proximity to Palforzia dosing when carers will be supervising the child, as justification for the lower expected use

of ambulance and A&E services. The company further note that a clinical expert validated the assumptions.

The ERG has some remaining concern that use of ambulance and A&E services for treatment related anaphylactic reactions may be downplayed somewhat relative to that for accidental exposures. Based on the ERG's expert clinical advice, it would be reasonable to assume that all anaphylactic reactions requiring adrenaline use should incur ambulance attendance and assessment in A&E. Therefore, the ERG assesses the impact of setting the resource use assumptions for treatment related anaphylactic reactions equal to those of accidental exposures requiring adrenaline. However, the same issue with respect to overestimating the unit cost of ambulance attendance also applies here, and the ERG explore the impact of revising this downward as described for accidental exposures above.

Costs associated with managing other (non-anaphylactic) moderate treatment related adverse events occurring in more than 5% of participants are also factored into the company model. Based on clinical expert advice, these were assumed to incur the cost of antihistamines and 10-minute phone call with an allergist (see Table 67 of the CS). The ERG further requested an analysis that incorporated the cost and utility implications for all moderate and severe adverse reactions, which the company provided in response to clarification letter (question B4). In this analysis, severe events were assigned the same cost as anaphylactic reactions to accidental exposures requiring adrenaline use – which as mentioned above may be overestimated due to the ambulance cost applied.

The ERG is satisfied that the costs associated with non-anaphylactic adverse events have been adequately captured in the model, and that they are not a key driver of cost-effectiveness.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company have provided an addendum to their submission document, updating information and tables from the CS with the new final agreed [redacted] list price for Palforzia. All analyses and model results reported in Chapters 5 and 6 of refer to the final agreed list price and cross reference to the company's addendum document where necessary.

QALYs and costs accrued in each model health state, are available in tables 57 and 59 of appendix J to the CS respectively. Information on the average time spent in each model health state for the base case analysis is available in Table 56 of appendix J to the CS. The company's data from the model outputs show that Palforzia QALY gains are driven primarily by a reduction in time spent in the avoidance "MTD:<300mg" state (Palforzia: 30.2 years; avoidance: 65.0 years), with a greater amount of time in the "peanuts in diet" state (Palforzia: 31.1 years; avoidance: 0.0 years).

The company's preferred base case deterministic and probabilistic ICERs are re-produced in Table 15. The preferred base case assumptions remained unchanged following clarification queries.

Table 15 Company base case deterministic and probabilistic ICERs (reproduced from Tables 70 and 71 of the Addendum to the CS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case analysis (deterministic)							
Palforzia	31,742	26.8	20.000	19,769	0.000	0.916	21,581
Avoidance	11,973	26.8	19.084				
Company base case analysis (probabilistic)							
Palforzia	33,979	--	20,011	22,060	--	0.948	23,270
Avoidance	11,919	--	19.063				

Scatter plots and CEACs from the company base case analysis are provided in figures 27 and 28, section 3.8.1 of the CS.

5.2 Company's sensitivity analyses

The company conducted a total of 12 scenario analyses, varying assumptions about time horizon (5,20 years), sources of clinical data (PALISADE or ARTEMIS), several assumptions about long-term outcomes elicited from the SHELF exercise (proportion and rate of transition to peanut in diet and subsequent return to avoidance), different sources and assumptions about utility parameters, and varying the number of carers. Scenario analyses are described in detail in Table 73 of the CS, with results provided in Table 74. The company also provide a tornado diagram illustrating the impact of varying the most important model parameters on the ICER.

The ERG notes that there is substantial uncertainty surrounding the base case ICER, with company conducted scenario analyses generating ICERs ranging from £10,712 to £42,163 per QALY gained. Unsurprisingly, the parameters which contributed the greatest uncertainty were the proportion of the cohort who discontinue Palforzia treatment and transition to peanuts in diet, as well as the subsequent assumptions about the proportion who transition from peanuts in diet to avoidance. Both parameters are highly uncertain and based on expert elicitation. Accordingly, utilities in both the MTD: <300mg and peanut in diet health states were important drivers of cost-effectiveness results. The ERG is satisfied that scenario analyses have been correctly implemented in the company economic model.

In addition to the scenario analyses provided in the company submission, the company provided 8 further scenario analyses in response to clarification queries (re-produced in Table 16).

Table 16 Scenario analyses conducted in response to clarification queries [reproduced from the Addendum to the CS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case analysis							
Palforzia	31,742	26.8	20.000	19,769	0.000	0.916	21,581
Avoidance	11,973	26.8	19.084				
Setting parameters for all tolerance health states equal to those in the 2000mg health state (further details in clarification response B1)							
Palforzia	32,338	26.8	20.044	20,053	0.000	0.905	22,170
Avoidance only	12,285	26.8	19.140				
Include all treatment related anaphylactic reactions							
Palforzia	31,889	26.8	20.000	19,916	0.000	0.916	21,743
Avoidance only	11,973	26.8	19.084				
Include all moderate and severe non-anaphylactic TRAEs							
Palforzia	31,823	26.8	19.999	19,849	0.000	0.915	21,684
Avoidance only	11,973	26.8	19.084				
Risk of accidental exposure based on PALISADE and ARC004 studies where possible (as opposed to from the risk quantification study)							
Palforzia	32,291	26.8	20.000	20.006	0.000	0.916	21,846
Avoidance only	12,285	26.8	19.084				
Include the costs of two food challenges added to initiation visit							
Palforzia	32,164	26.8	20.000	20,191	0.000	0.916	22,041
Avoidance only	11,973	26.8	19.084				
Utility in MTD: 300mg, 600mg, 1000mg, 2000mg tolerance states set equal to maintenance states prior to the food challenge, applied up to the last cycle of the 2nd year in the model.							
Palforzia	31,742	26.8	19.980	19,769	0.000	0.897	22,031
Avoidance only	11,973	26.8	19.082				

5.3 Model validation and face validity check

The ERG has quality assessed the model against the black-box checklist described by Tappenden and Chilcott 2014[50] and through additional face validity and a random selection of formulae checks in cells on the model trace. The findings of the ERG checks are provided in Table 17. No issues were identified.

Table 17 'Black box' verification checks conducted on the company base case model

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks, or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	• There are no differences in mortality benefit, therefore LYGs are equal across arms in all scenarios. • The model does not include measures of relative treatment effect. • Setting transition matrices and AEs for the avoidance arm equal to the Palforzia arm, discontinuation rates on Palforzia to 0 (to remove differential transitions to the "MTD: <300mg state" generates equal QALYS in both arms as expected. **No issues identified**
	Sum expected health state populations at any model time-point (state transition models)	Total probability equals 1.0	• Expected health state populations cross-checked in both arms across all time points. **No issues identified.**
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	• All patient HSUVs set equal to 1, general population utility adjustments removed, all carer disutility and adverse event disutility set equal to 0. QALY and LYGs equal as expected. **No issues identified**
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	• the company provided model traces do not include an assessment of undiscounted QALYs separately from the trace of discounted QALYs • Varying QALY discount has no impact on costs as expected. **No issues identified**

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	• Setting the discount rate to 100%, 1000%, 100,000% and 200,000% generates progressively lower QALYs in both model arms. **No issues identified**
Cost estimation	Set intervention costs to 0	ICER is reduced*	**No issues identified**
	Increase intervention cost	ICER is increased*	**No issues identified**
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	• the company provided model traces do not include an assessment of undiscounted costs separately from the trace of discounted costs • Varying cost discount has no impact on costs as expected. **No issues identified**
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	**No issues identified**
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.)	• Samples from all distributions checked **No issues identified.**

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	**No issues identified**
	Amend value of each individual model parameter*	ICER is changed	**No issues identified**
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	**No issues identified**
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has undertaken several further exploratory and sensitivity analyses to illustrate the impact of variation in different plausible assumptions on the ICER. Table 18 describes each of the analyses undertaken, together with a justification for each.

Table 18 ERG justification for additional exploratory and sensitivity analysis

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	Model structure				
1.	Utility assumptions after up-dosing, prior to the food challenge	Base case assumes tolerance dose will be known and utility of tolerance states applied prior to food challenge. Company scenario analysis assumes maintenance utility up to the point of the food challenge	**ERG preferred scenario:** As per company scenario analysis B8	ERG clinical expert opinion is that one food challenge will be completed, likely around 2 years. Exact tolerance levels will be unknown prior to this point, and so utility implications are unlikely to be realised.	4.2.2 4.2.7
2.	Treatment discontinuation due to a lack of tolerance	Palforzia treatment discontinuation all reasons (accidental exposure, adverse reactions and MTD:<300mg based on food challenge) prior to modelled food challenge time point.	**ERG preferred scenario:** Palforzia treatment discontinuation prior to food challenge only for accidental exposure and adverse reactions.	As per company base case, 1 food challenge will be used in clinical practice. ERG clinical expert opinion is that this would be around 2 years. It is therefore reasonable to assume that patients will remain on treatment up until the food challenge unless they experience adverse reactions or accidental exposure. Company clarification point: B7: [redacted] discontinued due to an MTD<300mg in PALISADE food challenge. The	4.2.2. 4.2.8.

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
				ERG assumes this fraction would remain on treatment from end of up-dosing to the point of the food challenge.	
	Utilities				
3.	Health state utility values obtained from company's *de novo* utility study	N=157 treatment naïve and treatment experienced respondents completing a mix of online survey and structured interview, with a mix of adolescent self-reported and carer proxy reported EQ-5D-Y for described health states.	**ERG preferred scenario:** N=38 treatment naïve adolescent respondents with experience of peanut allergy providing direct EQ-5D-Y responses to the described health states.	The ERG considers it more appropriate to model self-reported quality of life data where such data are available, even if the available sample is smaller. Furthermore, the ERG is concerned that some carer proxy reporting may reflect the impact of the condition on carers as well as children. Given that carer disutility is also included in the model, there is a risk of double counting in the company base case analysis.	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
4.	Up-dosing and maintenance utility in the avoidance arm of the model.	Up-dosing and maintenance specific utilities applied	**ERG preferred scenario:** Up-dosing and maintenance utilities set equal to MTD <300mg state	Including up-dosing and maintenance utilities does not reflect routine clinical practice where management is strict avoidance. In the absence of a food challenge, reasonable to assume utility equal to the avoidance state, current health with assumed MTD: <300mg.	4.2.2 4.2.7
5.	Utility of tolerance states in avoidance arm	Assumes that MTD is known, and associated utility implications incurred	**ERG preferred scenario**: Apply MTD: <300mg state utility across all other tolerance levels (with exception of spontaneous tolerance).	As most centers won't include a food challenge for patients on avoidance, the MTD will be unknown. Therefore, reasonable to assume utility implications equal to current health status from the utility study (i.e., MTD: <300mg).	4.2.7
6.	Peanuts in diet utility	Assumed equal to MTD: 2000mg state, regardless of the MTD achieved in the food challenge	**ERG exploratory scenario:** Assume utility equal to weighted average of MTD states achieved in the food challenge	The company approach assumes an instantaneous increase in utility upon inclusion of peanut in diet, that does not reflect the tolerance level observed from the food challenge and may be	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
				optimistic. The ERG scenario provides a more conservative estimate but is limited by assuming that tolerance will not increase over time.	
7.	Carer disutility	Assumes [redacted] carers incur disutility up to age 18	**ERG exploratory scenario:** Remove carer disutility	ERG provides this scenario to illustrate the impact of the decision whether to include carer disutility on the ICER	4.2.7
	Adverse reactions and accidental exposure treatments and resource use				
8.	Severe anaphylactic reactions	Excluded in base case, included in Scenario B3 in response to clarification	**ERG preferred scenario:** As per company scenario B3	Appropriate to include all anaphylactic reactions, even if occurrence is rare	4.2.8
9.	Moderate and severe TRAEs	Base case included those occurring in >5% of participants (Scenario analysis B4 in response to clarification included all)	**ERG preferred scenario:** As per company scenario analysis B4	Appropriate to consider all moderate and severe TRAEs that would likely incur resource use, even if occurrence is rare.	4.2.8
10.	Mild and moderate treatment related anaphylactic	Based on clinical expert opinion (assumed substantially lower resource use than accidental exposures requiring adrenaline)	**ERG preferred scenario:** Set equal to accidental exposure requiring adrenaline	ERG clinical expert view is that all cases that require adrenaline should be seen at hospital, incur ambulance, A&E costs with a proportion being	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	reaction resource use			admitted. As treatments for accidental exposure and adverse reactions are similar, resource use assumptions should reflect this.	
11.	Unit cost of ambulance transfer to hospital	Unit cost applied for ambulance use (£496.54), derived from a previously conducted ambulance service report, and inflated.	**ERG preferred scenario:** Apply the NHS reference cost (2018/19) ambulance services (ASS02, See and treat and convey) - £257)[49]	The company estimate double counts ambulance service costs. The ERG considers the use of reference cost data to be preferable wherever possible.	4.2.8

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 19 provides full details of the results of additional scenario analyses conducted by the ERG

Table 19 ERG additional scenario analyses results applied to the company's base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
0. Company base case analysis							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	31,742	26.8	20.000	19,769	0.000	0.916	21,581
1. Apply maintenance utility up to the timing of the food challenge							
Avoidance	11,973	26.8	19.082	-	-	-	-
Palforzia	31,742	26.8	19.980	19,769	0.000	0.897	22,031
2. Apply Palforzia treatment costs (i.e., remove discontinuation assumption) from end of up-dosing to timing of the food challenge							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	31,802	26.8	20.000	19,829	0.000	0.916	21,646
3. HSUVs based on self-reported data (adolescent sample, N=38)							
Avoidance	11,973	26.8	19.763	-	-	-	-
Palforzia	31,742	26.8	20.353	19,769	0.000	0.590	33,501
4. Remove up-dosing and maintenance utilities from avoidance arm (set equal to "MTD: <300mg" state)							
Avoidance	11,973	26.8	19.142	-	-	-	-
Palforzia	31,742	26.8	20.000	19,769	0.000	0.858	23,049
5. Set all HSUVs and carer disutility equal to current health state (i.e., MTD: "<300mg") in the avoidance arm							
Avoidance	11,973	26.8	19.056	-	-	-	-
Palforzia	31,742	26.8	20.000	19,769	0.000	0.944	20,931

6. Utility for "peanuts in diet" state set equal to a weighted average of MTD (300,600,1000,2000) states from the exit food challenge							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	31,742	26.8	19.859	19,769	0.000	0.775	25,510
7. Remove carer disutility							
Avoidance	11,973	26.8	19.480	-	-	-	-
Palforzia	31,742	26.8	20.226	19,769	0.000	0.746	26,484
8. Include severe anaphylactic reactions							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	31,889	26.8	20.000	19,916	0.000	0.916	21,743
9. Include all moderate and severe TRAEs							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	31,823	26.8	19.999	19,849	0.000	0.915	21,684
10. Set treatment related anaphylactic reaction = accidental exposure resource use							
Avoidance	11,973	26.8	19.084	-	-	-	-
Palforzia	32,749	26.8	20.000	20,776	0.000	0.916	22,680
11. Apply NHS reference costs for ambulance usage							
Avoidance	11,873	26.8	19.084	-	-	-	-
Palforzia	31,525	26.8	20.000	19,651	0.000	0.916	21,452

Abbreviations: HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTD: maximum tolerated dose (of peanuts) in mg; QALY: Quality adjusted life years; TRAE: treatment related adverse events

6.3 ERG's preferred assumptions

The ERG's preferred base case ICER incorporates the cumulative impact of the following assumptions:

- The ERG prefers assumptions where the HSUVs associated with a change in tolerance level are realised only after the results of a food challenge become known. The ERG's clinical expert opinion is that, in routine clinical practice, Palforzia treated patients would receive one follow-up food challenge at about 2 years, whereas avoidance patients would receive none (Scenarios 1, 4 and 5).

- The ERG also prefers an assumption that patients will continue with Palforzia treatment until the results of a food challenge become known, unless they have a TRAE or accidental exposure (Scenario 2).

- The ERG prefers HSUVs sourced directly from the adolescent (N=38) sub-sample of the company's *de novo* utility study who have experience of peanut allergy, as opposed to the company base case which combines adolescent self-reported and carer proxy (N=157). The ERG also considers direct valuation to minimize any risk of carer proxy double counting of their own disutility, which is included separately in the model (Scenario 3).

- The ERG prefers the inclusion of severe anaphylactic reactions and all moderate and severe TRAEs, even if event occurrences are rare (scenarios 8 and 9).

- The ERG prefers resource use for anaphylactic reactions that require adrenaline set equal the resource use associated with accidental exposures that require adrenalines. This applies an assumption across TRAEs and accidental exposures, whereby all patients that require adrenaline will also require an ambulance and a visit to A&E (Scenario 10).

- Finally, the ERG prefers the use of ambulance transfer unit costs sourced from NHS reference costs.

Individual changes to the ICER for each of the ERG's preferred assumptions have been reported in Table 19 above. The cumulative impact of each of the preferred changes to generate the ERG's preferred ICER is reported in Table 20. The deterministic and probabilistic ICER under the set of model assumptions preferred by the ERG is £36,565 and £39,716 per QALY gained respectively.

Table 20 ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company base-case	5.1	19,769	0.916	21,581
+ Apply maintenance utility up to the timing of the food challenge	4.2.2 4.2.7	19,769	0.897	22,031
+ Apply Palforzia treatment costs (i.e., remove discontinuation assumption) from end of up-dosing to timing of the food challenge	4.2.2 4.2.8	19,829	0.897	22,097
+ HSUVs based on self-reported data (adolescent sample, N=38)	4.2.7	19,829	0.577	34,376
+ Remove up-dosing and maintenance utilities from avoidance	4.2.2 4.2.7	19,829	0.541	36,641

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
arm (set equal to "MTD: <300mg" state)				
+ Set all HSUVs and carer disutility equal to current health state (i.e., MTD: "<300mg") in the avoidance arm	4.2.7	19,829	0.560	35,393
+ Include severe anaphylactic reactions	4.2.8	19,975	0.560	35,660
+ Include all moderate and severe TRAEs	4.2.8	20,056	0.559	35,847
+ Set treatment related anaphylactic reaction = accidental exposure resource use	4.2.8	21,063	0.559	37,647
+ Apply NHS reference costs for ambulance usage	4.2.8	20,458	0.559	36,565
ERG preferred deterministic ICER (Combination of all scenarios above)	**6.3**	**20,458**	**0.559**	**36,565**
ERG preferred probabilistic ICER (Combination of all scenarios above)	**6.3**	**22,738**	**0.573**	**39,716**

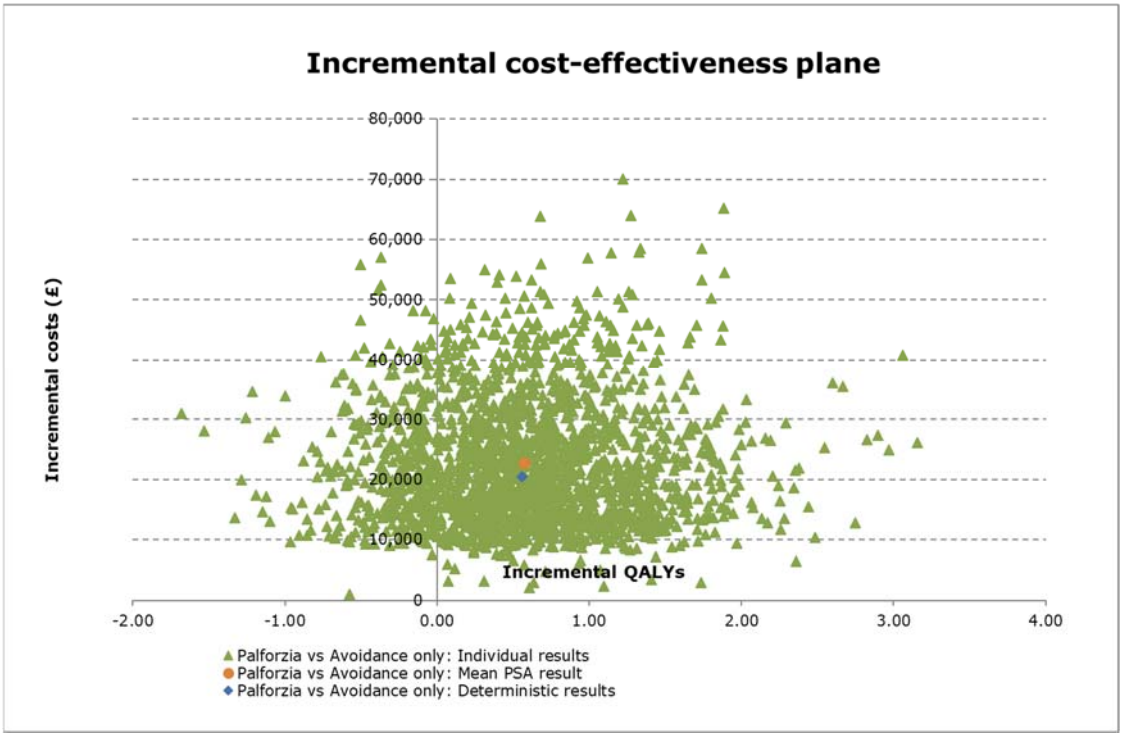


Figure 8 Scatter plot of cost-effectiveness plane using ERG preferred base case ICER [reproduced directly from the company submitted economic model]

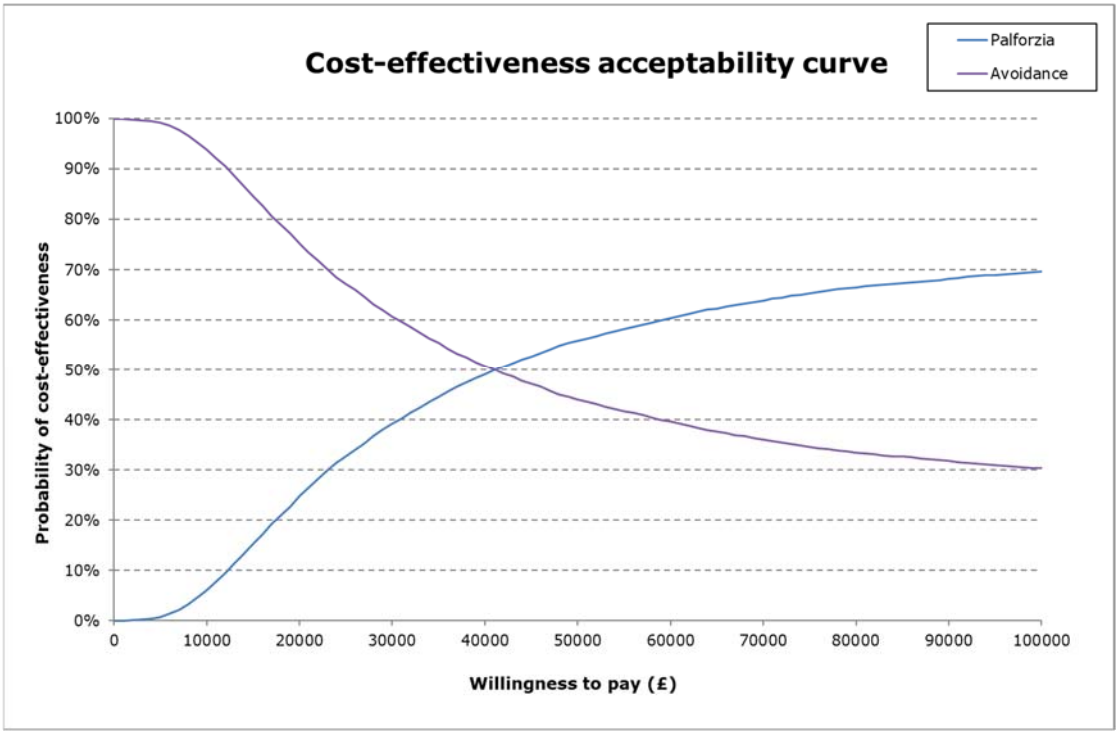


Figure 9 Cost-effectiveness acceptability curve using ERG preferred base case ICER [reproduced directly from the company's submitted economic model]

Scenario analyses applied to the ERG preferred base case

Table 21 Scenario analyses applied to ERG preferred base case

Assumption	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company base-case	19,769	0.916	21,581
ERG base-case	20,458	0.559	36,565
Time horizon (5 years)	9,285	0.135	68,613
Time horizon (8 years – to age 18)	10,503	0.248	42,373
Time horizon (20 years)	14,286	0.373	38,311
Discounting of costs and benefits - 0%	43,562	1.251	34,834
Discounting of costs and benefits - 6%	15,566	0.397	39,222
ARTEMIS population	19,483	0.535	36,394
Transition to inclusion of peanut in diet = low value ([redacted]	28,659	0.577	49,626
Transition to inclusion of peanut in diet = high value ([redacted]	14,991	0.547	27,381
Transition to inclusion of peanut in diet = mean across all participating clinicians in SHELF elicitation exercise ([redacted]	25,242	0.570	44,284
Transition from peanuts in diet to avoidance = low value ([redacted]	20,541	0.603	34,087
Transition from peanuts in diet to avoidance = high value ([redacted])	20,351	0.504	40,386
Remove carer disutility	20,458	0.434	47,119

Utility for "peanuts in diet" state set equal to a weighted average of MTD (300,600,1000,2000) states from the exit food challenge	20,458	0.530	38,615

6.4 Conclusions of the cost effectiveness section

The company's base case ICER is £21,581 per QALY gained and remained unchanged following response to clarification queries. The ERG preferred ICER (£36,565 per QALY gained) assumes:

1) That treatment discontinuation or realisation of the utility benefits of improved tolerance can only be realised after a single food challenge in the Palforzia arm, and that there would be no food challenges in clinical practice for patients treated by avoidance only.
2) That HSUVs based on EQ-5D-Y responses provided directly by adolescents with experience of peanut allergy are more appropriate than carer proxy responses.
3) That all TRAE and anaphylactic reactions should be included, that the resource use associated with all events requiring adrenaline should be equal and that the cost of ambulance transfer for these events should be sourced from NHS reference costs.

The company and ERG conducted a range of scenario analyses illustrating that the ICER was most sensitive to assumptions about the proportion of Palforzia treated patients who will discontinue treatment to include peanuts in their diet, achieving utility gains alongside the removal of treatment acquisition costs. The ICER was also sensitive to assumptions about the proportion who revert from inclusion of peanut in diet back to the semi-absorbing long-term avoidance state. Both parameters were based on a clinical expert elicitation exercise and are surrounded by considerable uncertainty. These parameters impact on the ICER by determining the proportion of the cohort who can achieve long-term benefits of Palforzia treatment (over a lifetime) without incurring ongoing treatment acquisition costs. Uncertainty surrounding the

magnitude of utility difference between avoidance (MTD:<300mg) and inclusion of peanuts in diet further widens the range of potentially plausible ICERs. The ERG therefore considers it difficult to determine a definitive estimate of the most plausible ICER, but it is likely to be higher than £30,000 per QALY gained.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Palforzia for treating peanut allergy [ID1282]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 10 August** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Incorrect data or information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, page 3, paragraph 3 Incorrect information	The company prefers patient quality of life obtained from a mix of adolescent reported (N=40) and carer proxy (N=117) reported data.	The study was conducted with a sample of N=40 adolescents (38 of whom were treatment naïve, 2 were treated with Palforzia) and N=117 parents/ guardians of children with peanut allergy	Numbers amended to 40 adolescents and 117 carers, respectively.
Section 2.3, page 16, Table3, row 2, column 6 Incorrect information	'Anticipated' should be amended to 'Final'	The indication has been finalised.	Text amended as suggested.
Section 3.2.2, page 34, Table 7, row 11 ('North America'), column 2 (PALISADE, Palforzia group) Incorrect data	'[redacted]' should be amended to '[redacted]'	Typographical error	The typographical error has been amended.
Section 3.2.2, page 34, Table 7, row 11 ('North America'), column 4 (ARC004 cohort 1) Incorrect data	'[redacted]' should be amended to '[redacted]'	Demographic information for ARC004 are reported by country. Participants from Canada should be listed in the row for 'North America', not 'Other'.	Text amended as suggested.
Section 3.2.2, page 34, Table 7, row 11 ('North America'), column 5 (ARC004 cohort 3A) Incorrect data	'[redacted]' should be amended to '[redacted]'	Demographic information for ARC004 are reported by country. Participants from Canada should be listed in the row for 'North America', not 'Other'.	Text amended as suggested.

Section 3.2.2, page 34, Table 7,row 12 ('UK'), column 5 (ARC004 cohort 3A) Incorrect data	'[redacted]' should be amended to '[redacted]'	Typographical error	The typographical error has been amended.
Section 3.2.2, page 34, Table 7, row 13 ('Europe'), column 4 (ARC004 cohort 1) Incorrect data	'[redacted]' should be amended to '[redacted]'	Demographic information for ARC004 are reported by country. Number of participants from Europe can be calculating by summing participants from the European countries (excluding UK, in alignment with data reported by the ERG for ARTEMIS).	Text amended as suggested.
Section 3.2.2, page 34, Table 7, row 13 ('Europe'), column 5 (ARC004 cohort 3A) Incorrect data	'[redacted]' should be amended to '[redacted]'	Demographic information for ARC004 are reported by country. Number of participants from Europe can be calculating by summing participants from the European countries (excluding UK, in alignment with data reported by the ERG for ARTEMIS).	Text amended as suggested.
Section 3.2.2, page 34, Table 7, row 14 ('Other') Incorrect data	This row should be deleted.	Demographic information for ARC004 and ARTEMIS are reported by country. As study sites were only in North America (USA and Canada) and in European countries, these participants can be accounted for in the categories for 'North America' and 'Europe'. No	Text amended as suggested.

		participants were enrolled in other world regions.	
Section 3.2.2, page 38, Table 9, row 3 (‘Tolerance of 1000 mg’), column 8 (ARC001 Palforzia group) Incorrect data	’62.0’ should be amended to ‘NR’	The highest dose possible in the ARC001 study was 600 mg (1043 cumulative), therefore the primary endpoint was tolerance of 600 mg, not 1000 mg. Information for the 1000 mg endpoint should be moved to the rows for the 600 mg endpoint. All values for 1000mg should be ‘NR’	Text amended as suggested.
Section 3.2.2, page 38, Table 9, row 5 (‘Tolerance of 600mg mg’), column 8 (ARC001 Palforzia group) Incorrect data	‘NR’ should be amended to ’62.0’	The primary endpoint was tolerance of 600 mg, not 1000 mg. Information for the 1000 mg endpoint should be moved to the rows for the 600 mg endpoint. Information for the 1000 mg endpoint should be moved to the rows for the 600 mg endpoint	Text amended as suggested.
Section 3.2.2, page 38, Table 9, row 3 (‘Tolerance of 1000 mg’), column 9 (ARC001 placebo group) Incorrect data	‘0.0’ should be amended to ‘NR’	The highest dose possible in the ARC001 study was 600 mg (1043 cumulative), therefore the primary endpoint was tolerance of 600 mg, not 1000 mg. All values for 1000mg should be ‘NR’	Text amended as suggested.
Section 3.2.2, page 38, Table 9, row 5 (‘Tolerance of 1000 mg’),	‘NR’ should be amended to ‘0’	The highest dose possible in the ARC001 study was 600 mg (1043	Text amended as suggested.

column 9 (ARC001 placebo group) Incorrect data		cumulative), therefore the primary endpoint was tolerance of 600 mg, not 1000 mg. Information for the 1000 mg endpoint should be moved to the rows for the 600 mg endpoint	
Section 3.2.2, page 38, Table 9, row 5 ('Tolerance of 600 mg'), column 5 (ARC004 cohort 3A) Incorrect data	'80.4 (99.9)' should be amended to '96.2 (80.4, 99.9)'	Data incorrectly copied from CS, Document A Section A.7.2 Table 5.	Text amended as suggested.
Section 3.2.2, page 41, paragraph 1, last line Incorrect information	'accidental exposure to peanut' should be amended to 'accidental food allergen exposure'	The treatment requirement and epinephrine data in Table 63 of the ARC004 CSR are for all accidental food allergen exposure, not only peanut.	Text amended as suggested.
Section 4.1, page 53, paragraph 2 Incorrect information	The search strategy was not limited by language or date restrictions and searches were conducted up to January 2021.	The search strategy was not limited by language, however non-English language articles were excluded during abstract selection.	Text has been amended to clarify that non-English language articles were excluded during abstract selection.
Section 4.2.6, page 65, paragraph 4 Incorrect information	'The experts advised that most patients in the UK would likely switch to regular inclusion of peanut in their diet from [redacted] years instead of continuing with Palforzia treatment.' Should be amended to: 'The experts advised that most patients in the UK would likely switch to regular inclusion of peanut in their diet after [redacted] years instead of continuing with Palforzia treatment'	The switch to peanuts was implemented after [redacted] years of Palforzia treatment, at the beginning of [redacted] year.	Text amended as suggested.
Section 4.2.6, page 65, paragraph 4	'at [redacted] years' should be amended to 'after [redacted] years of Palforzia treatment (i.e., at beginning of year	The switch to peanuts was implemented after [redacted] years of Palforzia treatment, at the	Text amended as suggested.

Section 4.2.6, page 66, paragraph 1 Incorrect information	[redacted])'	beginning of [redacted] year.	
Section 4.2.6, page 67, paragraph 2 Incorrect data	'(0/19) should be amended to '(0/24)'	Rate 0/19 provided for Palforzia reflects number of reactions required treatment with adrenaline during up-dosing period only, while rate 3/13 provided for placebo reflects number of reactions required treatment with adrenaline during overall study period. For consistency we suggest replacing 0/19 rate by 0/24.	Text amended as suggested.
Section 5.2, page 86, Table 16, row 6, column 4 Incorrect data	'20.045' should be amended to '20.044'	Data incorrectly copied from the model.	Text amended as suggested.
Section 6.1, page 95, Table 18, Analysis number 7 Incorrect data	'[redacted]' should be amended to '[redacted]	Data incorrectly copied from the CS.	Text amended as suggested.
Section 6.2, page 97, Table 19, Analysis number 5 Incorrect data	'19.117' should be amended to '19.056'	Data incorrectly copied from the model.	Text amended as suggested.
Section 6.2, page 98, Table 19, Analysis number 9 Incorrect data	'20.000' should be amended to '19.999'	Data incorrectly copied from the model.	Text amended as suggested.

Issue 2 Missing information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.2, page 35, Table 7, last row, column 8 (ARC001 Palforzia group) Missing superscript letter 'i' for footnote	'(24.1)' should be amended to '(24.1)[i]'	The footnote is required to denote that this this is other allergy, including food or drug allergy. This footnote is required for the accuracy of data specific to the ARC001 study.	Text amended as suggested.
Section 3.2.2, page 35, Table 7, last row, column 9 (ARC001 placebo group) Missing superscript letter 'i' for footnote	'(15.4)' should be amended to '(15.4)[i]'	The footnote is required to denote that this this is other allergy, including food or drug allergy. This footnote is required for the accuracy of data specific to the ARC001 study.	Text amended as suggested.
Section 3.2.2, page 35, footnotes below table 7 Missing footnote	The footnote should be inserted before '*ARC001' and read '[i]Reported as other allergy (including other food or drug allergy)'	The footnote is required to denote that this this is other allergy, including food or drug allergy. This footnote is required for the accuracy of data specific to the ARC001 study.	Footnote has been added as suggested.
Section 3.2.2, page 38, Table 9, row 6, columns 8-9 Missing P-value	'p<0.0001' should be entered in the cell, below 'NR'	As reported in the publication for the difference between groups in the tolerance of 600 mg.	Text amended as suggested.
Section 3.2.2, page 44, paragraph 1 Missing information in sentence	'in the completer population of PALISADE' should be amended to 'in the ITT and completer populations of PALISADE'	To accurately reflect the information provided in the company submission (Appendix E1.1)	Text amended as suggested.

Section 3.2.2, page 44, paragraph 1 Missing information in sentence	'ARTEMIS ITT population' should be amended to 'ARTEMIS ITT and completer populations'	To accurately reflect the information provided in the company submission (Appendix E1.2)	The text in the ERG report refers to the information reported on page 93 of the CS. Not a factual error.
Section 4.2.7, page 78, Table 14, row 11, column 4 Missing footnote	The footnote should be inserted to explain abbreviation 'C'	Abbreviation was used in the table but was not defined.	The footnotes have been revised to make clear the source of HSUVs for the ERG's preferred case - Table 9 of Appendix P to the CS.
Section 5.1, page 84, paragraph 2 Missing number of an appendix	'QALYs and costs accrued in each model health state, are available in tables 57 and 59 of the appendix to the CS respectively' should be amended to 'QALYs and costs accrued in each model health state, are available in tables 57 and 59 of the appendix J to the CS respectively'	Number of the appendix is missing	Text amended as suggested. Have also amended the following sentence to indicate that Table 56 is also from appendix J of the CS.

Issue 3 Incorrect text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.2, page 41, paragraph 1, lines 3-4 Incorrect sentence	'requirement for accidental exposure to peanut requiring treatment was' should be amended to 'rates of accidental exposure to peanut requiring treatment were'	The current sentence is incorrect	Text amended as requested.

Issue 4 Confidentiality mark up missing

Location of incorrect marking	Description of incorrect marking	Justification for amendment	ERG response
Section 3.2.2, page 35, footnotes below table Confidentiality mark up missing	‘[redacted] and [redacted]’ needs to be marked as confidential‘[redacted] and [redacted]’	CIC markup is currently missing	CIC markup has been added.
Section 3.2.2, page 35, footnotes below table Confidentiality mark up missing	‘[redacted] and [redacted]’needs to be marked as confidential ‘[redacted] and [redacted]’	CIC markup is currently missing	CIC markup has been added.
Section 3.2.3, page 45, paragraph 1 Confidentiality mark up missing	‘difference between Palforzia and placebo was [redacted]’ should be amended to ‘difference between Palforzia and placebo was [redacted]’	AIC markup is currently missing	AIC markup has been added.
Section 3.2.3, page 45, paragraph 1 Confidentiality mark up missing	‘remained [redacted]’ should be amended to ‘remained [redacted]’	AIC markup is currently missing	AIC markup has been added.
Section 3.2.3, page 45, paragraph 1 Confidentiality mark up missing	‘placebo was [redacted]’ should be amended to ‘placebo was [redacted]’	AIC markup is currently missing	AIC markup has been added.
Section 4.2.6, page 65, paragraph 4	‘The experts advised that most patients in the UK would likely switch to regular inclusion of peanut in their diet from [redacted] years instead of continuing with Palforzia treatment.’ should be amended to ‘The experts advised that most	AIC markup is currently missing	AIC markup has been added.

	patients in the UK would likely switch to regular inclusion of peanut in their diet from [redacted] years instead of continuing with Palforzia treatment.'		
Section 4.2.7, page 72, paragraph 1	'EQ-5D-Y in an adolescent population to the same health states in both the adult population (i.e., in cycles after the cohort age turns 18) and for children aged [redacted], the ERG accepts that the company's approach is reasonable' should be amended to 'EQ-5D-Y in an adolescent population to the same health states in both the adult population (i.e., in cycles after the cohort age turns 18) and for children aged [redacted], the ERG accepts that the company's approach is reasonable'	AIC markup is currently missing	AIC markup has been added.
Section 6.1, page 95, Table 18, Analysis number 7	'Assumes [redacted] carers incur disutility up to age 18' should be amended to 'Assumes [redacted] carers incur disutility up to age 18'	AIC markup is currently missing	AIC markup has been added.

Issue 5 Removal of confidentiality mark up

Location of incorrect marking	Description of incorrect marking	Justification for amendment	ERG response
Section 3.2.2, page 38, Table 9,	Data in rows for 'None', 'Mild', 'Moderate', 'Severe or higher' and 'P-value'	Remove AIC marking. This information	AIC marking has been removed

rows 10-14, columns 5 and 6 (ARC004 Cohort 1 and Cohort 3A)		is visible in the publication figure.	.
Section 3.2.2, page 43, paragraph 1	The AIC mark up for the following sentence can be removed. ‘[redacted].’	Remove AIC marking. This information has now been published.	AIC marking has been removed.
Section 3.2.2, page 44, Figure 4	AIC mark up for Figure 4 can be removed	Remove AIC marking. The cited paper has now been published.	AIC marking has been removed.

Issue 6 Minor incorrect data / information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table of abbreviations, page 10, row 20 Incorrect abbreviation in Table of Abbreviations	The row for 'IL Interleukin' should be deleted	The abbreviation is not used in the ERG report. No impact	The row for 'IL Interleukin' has been deleted.
Table of abbreviations, page 10, row 23, column 1 Incorrect abbreviation in Table of Abbreviations	'MCID' should be amended to 'MID', and moved down in the table after 'MED'	The abbreviation MCID is not used in the ERG report, but rather it is reported as 'MID'.	MCID has been amended to MID.
Table of abbreviations, page 10, row 23, column 2 Incorrect abbreviation in Table of Abbreviations	'Minimally clinically important difference' should be amended to 'Minimally important difference'	The abbreviation MCID is not used in the ERG report, but rather it is reported as 'MID'.	Text amended as suggested.
Section 3.2.1, page 29, abbreviations below table 6 Incorrect abbreviation below table	'NHLBI: National Heart, Lung, and Blood Institute;' should be deleted	Abbreviation is not used in the table	NHLBI: National Heart, Lung, and Blood Institute has been deleted from the footnote.
Section 3.2.2, page 34, Table7, row 16, column 8 (ARC001 Palforzia group) Incorrect data	'>' should be amended to '≥'	As reported in the publication.	Symbol amended as suggested.
Section 3.2.2, page 34, Table 7, row 16, column 9 (ARC001	'>' should be amended to '≥'	As reported in the publication.	Symbol amended as suggested.

placebo group) Incorrect data			
Section 3.2.2, page 44, footnote below Figure 4 Updated information	'Fernandez-Rivas et al., 2021 submitted manuscript' should be amended to 'Fernandez-Rivas et al., 2021'	The submitted manuscript has been published.	Footnote amended as suggested.
Section 3.2.4, page 47, abbreviations below table 10 Incorrect abbreviation below table	'SAE: serious adverse event;' should be deleted	Abbreviation is not used in the table	Abbreviation deleted from footnote as suggested.
Section 5.1, page 85, paragraph 1 Incorrect reference	'Scatter plots and CEACs from the company base case analysis are provided in 27 and 28, page 170 of the CS.' should be amended to 'Scatter plots and CEACs from the company base case analysis are provided in figures 27 and 28, pages 167 and 168 of the CS.'	Incorrect reference to the CS	Page numbering can vary based on printing configurations. To avoid potential for confusion, we have removed the page number reference and provided the report section (3.8.1) instead.

Issue 7 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, page 2, paragraph 1, line 2 Typographical error	'trial' should be amended to 'trials'	Minor typographical error	The minor typographical error has been amended.
Section 1.5, page 6, Issue 1 table, row 4, column 2	("MTD: <300mg) should be amended to ("MTD: <300mg")	Minor typographical error	The minor typographical error has been amended.
Section 2.2, page 13, paragraph	'refers' should be amended to 'refer'	Minor typographical error	The minor typographical error

2, line 1 Typographical error			has been amended.
Section 2.2, page 13, paragraph 3, line 8 Typographical error	‘100,00’ should be amended to ‘100,000’	Minor typographical error	The minor typographical error has been amended.
Section 2.3, page 16, row 1, column 5 Typographical error	‘that population’ should be amended to ‘that the population’	Minor typographical error	The minor typographical error has been amended.
Section 2.3, page 19, row 2 column 5 Typographical error	‘matches’ should be amended to ‘match’	Minor typographical error	The minor typographical error has been amended.
Section 3.2.2, page 43, paragraph 1 Typographical error	‘from baseline of at’ should be amended to ‘from baseline at’	Minor typographical error	The minor typographical error has been amended.
Section 3.2.4, page 46, paragraph 1 Typographical error	‘TEAEs are defined in’ should be amended to ‘TEAEs are defined as’	Minor typographical error	The minor typographical error has been amended.
Section 3.2.4, page 46, paragraph 3 Typographical error	‘July 31, 2020’ should be amended to ‘July 31, 2020)’	Minor typographical error	The minor typographical error has been amended.
Section 3.3, page 50, paragraph 5 Typographical error	‘further RCT which’ should be amended to ‘further RCT, which’	Minor typographical error	The minor typographical error has been amended.

Section 4.2.2, page 58, paragraph 1	'PALISDE' should be amended to 'PALISADE'	Minor typographical error	The minor typographical error has been amended.
Section 4.2.6, page 65, paragraph 3 Typographical error	'onion' should be amended to 'opinion'	Minor typographical error	The minor typographical error has been amended.
Section 4.2.6, page 70, paragraph 2	'TREAs' should be amended to 'TRAEs'	Minor typographical error	The minor typographical error has been amended.
Section 5.1, page 84, paragraph 2 Typographical error	'palforzia QALY' should be amended to 'Palforzia QALY' 'palforzia: 31.1 years' should be amended to 'Palforzia: 31.1 years'	Minor typographical error	The minor typographical errors have been amended.
Section 5.1, page 85, paragraph 1 Missing word	'Scatter plots and CEACs from the company base case analysis are provided in 27 and 28' should be amended to 'Scatter plots and CEACs from the company base case analysis are provided in figures 27 and 28'	Word 'figures' missing	Word 'figures' as been added as suggested.
Section 5.2, page 86, Table 16	'reeproduced' should be amended to 'reproduced'	Minor typographical error	The minor typographical error has been amended.
Section 5.3, page 88, Table 17, row 2, column 4	'palforzia' to be amended to 'Palforzia'	Minor typographical error	The minor typographical error has been amended.
Section 6.4, page 104, paragraph 2	'palforzia' to be amended to 'Palforzia'	Minor typographical error	The minor typographical error has been amended.

Issue 8 Missing abbreviations in the list of abbreviations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
List of abbreviations, page 10 Abbreviation missing from table	The following abbrevations need to be added to the abbreviations table 'CI Confidence Interval', 'CRD Centre for Review and Dissemination', CSR Clinical study report', 'FDA US Food and Drug Administration', 'GI Gastrointestinal', 'IDE Initial dose escalation', 'IPD Individual participant data', 'N/A Not applicable', 'NHS National Health Service', 'NMA Network meta-analysis', 'NR Not reported', 'PSS Personal Social Services', 'Q Quartile' and 'TSQM-9 Treatment Satisfaction Questionnaire for Medication-9'	Missing abbreviation used in the ERG report but missing from the list of abbreviations	Text amended as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Palforzia for treating peanut allergy [ID1282]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **20 September 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Aimmune**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Timing of food challenges including the timing at which utility gains are realised in clinical practice	**NO**	Upon further consideration, Aimmune agrees with the ERG position that only one food challenge is likely to be offered after completing Palforzia up-dosing in clinical practice and no food challenge would be offered to patients following peanut avoidance only. Aimmune also agrees it is logical that utility gains related to knowing the number of peanuts a patient can tolerate can only be realized once a food challenge has been performed and the patient and their carer(s) informed. In Aimmune's opinion the likely timing of the food challenge for Palforzia patients would be between 1 and 2 years after starting treatment. Aimmune therefore accepts that 2 years is an acceptable if conservative assumption for when the food challenge may occur and the related utility gains would be realised. Finally, Aimmune agrees it is logical that patients following peanut avoidance only would maintain the same utility value of MTD<300mg throughout the tolerance health states, given they would not be likely to have a food challenge in clinical practice.
Key issue 2: Long term assumptions about treatment discontinuation, and transition from peanuts in	**NO**	**1. Transition to peanuts in diet relies on the opinion of one clinical expert, rather than all included in the SHELF.** Aimmune wishes to clarify that the proportion of patients transitioning to peanuts in diet used in the Palforzia economic model (SHELF parameter P1: the proportion of patients who, having completed [redacted] years of treatment on Palforzia, will ever transition off Palforzia and on to consuming peanuts in their diet) was chosen by the group of [redacted] UK clinical experts who participated in the SHELF physician elicitation exercise. The SHELF process involves experts firstly eliciting their own individual judgements, then arriving at an aggregate group consensus judgement through subsequent facilitated discussion and debate. In considering what this consensus judgement should be, the experts are asked to consider what a 'rational, impartial observer' would think, having heard all the discussion. It

diet to avoidance.		is quite common for some experts to modify their initial probability judgements, having heard the views of others; mathematical aggregation of the initial judgements may not reflect such changes. In the Palforzia SHELF exercise, after each of the [redacted] experts provided their own individual estimates for P1, the experts debated the question and related evidence, and [redacted] experts subsequently stated that they would increase their estimates for P1 based on the debate. The facilitator made a suggestion to the group to adopt one expert's distribution as the consensus distribution, as it broadly reflected the range of expert individual judgements after several experts had adjusted their estimates. The experts agreed with this proposal. **2. The validity and derivation of the weighting of responsibility ([redacted] carers / [redacted] patients) for ensuring adherence to peanut in diet is unclear.** Aimmune wishes to clarify that the weighting of responsibility for ensuring adherence to peanut in diet was chosen by the SHELF clinical experts. In discussing how to estimate parameter P2 (i.e. the proportion of patients who, having switched to peanut in diet, subsequently will ever revert to avoidance only) the clinical experts considered this parameter would be driven by the adherence behaviours of the patients and their families. The experts believed this proportion would be lower for younger children or those whose parents took responsibility for their regular intake of native peanut, than for teenagers or for those patients with limited parental oversight. The facilitator advised the experts that they could, if preferred, break down P2 into two groups of patients and elicit the unknown parameter for each group in turn (the two parameters to be referred to as P2A and P2B). The experts debated whether the main driver of adherence would be the patient's age or the level of parent/carer responsibility for their regular intake of peanut in diet. The experts subsequently chose to vote on whether to estimate P2A and P2B split by age, split by responsibility for peanut intake or to estimate P2 as a whole without breaking down into groups A and B. The majority ([redacted]) favoured estimating P2A and P2B based on level of carer versus patient responsibility for maintaining peanut in diet, noting that families who successfully reach maintenance dosing are generally very motivated, and that some teenagers would have motivated parents still overseeing their peanut consumption ([redacted] experts favoured estimating P2A and P2B by age, and the remaining [redacted] experts would have preferred to estimate P2 as a whole). Based on their clinical judgement and patients in their care, the experts estimated that for approximately [redacted] of patients, parents/carers would be responsible for their regular peanut intake and for the remaining [redacted] of patients, the patients would be

		responsible for this. Specifically, two experts proposed [redacted] parent/carer responsibility, and another expert suggested [redacted] with the remaining experts concurring. **3. Assumption that no further transition from "peanut in diet" to avoidance would be expected longer-term, particularly around the time where children become responsible for their own adherence.** In estimating P2, the experts were asked to estimate the proportion of patients who would ever transition from peanut in diet to peanut avoidance at any time. The experts also discussed over what time period patients reverting from peanut in diet to peanut avoidance would do so (modelling assumption T2). They believed most patients who were ever going to revert to peanut avoidance would have done so by [redacted] years after transitioning onto peanut in diet. The experts noted that there could be some further reversion to peanut avoidance beyond this timepoint e.g., if the patient's regular peanut consumption were interrupted for some reason such as an accident or hospital stay but considered the likely level to be low. For simplicity of incorporation in the model, this transition from peanut in diet to peanut avoidance was assumed to occur over [redacted] years on a straight-line basis. In reality, the transition may be more of a curve than a straight line, but Aimmune anticipates this added level of detail would not impact the ICER significantly. Moreover, if the transition to avoidance were to occur over a longer period, this would likely reduce the ICER as patients would retain the utility benefits of having peanuts in their diet for longer. The model allows the user to change T2, and in Aimmune's base case model, e.g., changing T2 from [redacted] years to [redacted] years reduces the ICER from £21,581 to £21,387.
Key issue 3: Patient health state utility values	**YES**	Aimmune agrees with the ERG that it is important to elicit EQ-5D responses directly from patients wherever possible. However, where it is not possible as in the case of younger children with peanut allergy, Aimmune believes that the caregiver proxy-reported values are valid and in line with the NICE reference case. On this subject, section 5.3.3 of the NICE reference case states "Health-related quality of life, or changes in health-related quality of life, should be measured directly by patients. When it is not possible to obtain measurements of health-related quality of life directly from patients, data should be obtained from the person who acts as their carer [in preference to healthcare professionals]". [redacted]

In light of the challenges of utility measurement in children and adolescents, and a lack of consensus or guidelines around when and at what age self-report and proxy-report administrations should be used, Aimmune believes that, where feasible, both self- and caregiver proxy-reported utility values should be collected and presented, to provide a holistic view and reduce uncertainty. Aimmune therefore disagrees with the ERG's preferred approach of only considering the relatively small sub-sample of n=38 adolescent self-reported EQ-5D values to estimate HSUVs for the whole population and excluding the remaining n=117 caregiver proxy reported sample, and believes that the caregiver proxy-reported values were valid.

As evidence of this, Table 9, Appendix P, page 261 of the Company Submission (Document B) shows that for the sample of n=38 adolescents who provided their own EQ-5D ratings, caregiver and self-reported HSUVs were highly aligned, and in fact caregivers reported a slightly lower mean benefit of successful treatment than the adolescents (a difference of [redacted] between 'tolerate 6-8 peanuts' and 'current HRQoL', whereas for adolescents the difference was [redacted]). This would suggest that the ERG's concern of caregivers double-counting their own concern and anxiety in their responses on behalf of their children is unfounded.

Document B, Table 9, Appendix P, p261, Treatment naïve survey: adolescent EQ-5D: Self-report and caregiver proxy report (N=38)

	Child			Caregiver		
	Index Mean (SE)	Difference	VAS Mean (SE)	Index Mean (SE)	Difference	VAS Mean (SE)
Current HRQoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Furthermore, although the FAQLQ disease specific HRQL data collected in the Palforzia clinical trials were not used to derive HSUVs in the Palforzia model, the results provide further evidence of the validity of caregiver proxy reported values in children with peanut allergy.
Table 18 of Document B, section B2.6.4 (page 83) presents the mean change from PALISADE baseline in FAQLQ scores by the end of the ARC004 follow-on study after 1.5-2 years treatment, for both cohorts 1 and 3A that were used in the model. When comparing self- and caregiver proxy reported FAQLQ scores by age group (8-12 self-report versus 7-12 proxy report, and 13-17 self and proxy report), proxy values were similarly aligned with the patients' self-reported values, and again in several cases reporting a slightly lower mean HRQL gain than the patients. (In cohort 1, patients aged 8-12 years reported an improvement

(i.e., reduction) of [redacted] in their FAQLQ score, whereas the caregiver proxy reported improvement was [redacted]. Similarly, patients aged 13-17 in cohort 1 reported an improvement of [redacted], compared to [redacted] caregiver proxy-reported improvement for the same age range. In the somewhat smaller cohort 3A, similar alignment was seen between self and proxy reported values in the 13-17 age group [redacted] versus [redacted]), but caregivers for age range 7-12 years reported less improvement than the patients themselves ([redacted] reported by patients, [redacted] by parents). Therefore, it does not appear to be the case that caregivers have overstated the burden of peanut allergy or benefit of treatment in their children.

Excerpt from table 18, Document B, p83: PALISADE follow-on (ARC004) FAQLQ mean change from baseline in total score in participants aged 4 to17 years (safety population)

	Cohort 1	Cohort 3A
FAQLQ Total Score		
Self-reported, participants 8–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Self-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 4–6 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 7–12 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Parent proxy-reported, participants 13–17 years	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]

Given proxy and self-reported values for adolescents in the utility survey are very similar, this suggests that the proxy is a reasonable estimate of adolescent HRQL. Moreover this suggests that the larger utility gain from successful treatment and tolerating 6-8 peanuts seen in the survey results overall is not due to caregivers overstating their child's burden or benefit of treatment, rather it is mostly due to the different sample methodologies used, [redacted]

		[redacted] The [redacted] difference in HSUV value between 'tolerate <300mg/avoidance only' and 'tolerate 6-8 peanuts' health states used in the base case model compares very similarly to other modelling estimates and literature. For example, a difference in utility of 0.06 was assumed between patients in the sensitized and desensitized health states in the ICER model of Palforzia, independently developed by researchers at the University of California. In terms of disease proxies, it also aligns with research suggesting the HRQL burden of children with PA is greater than for children with T1DM. (The Global Burden of Disease survey 2019 assumes a disability weight of 0.049 to calculate DALYs for uncomplicated T1DM. (see Global Burden of Disease Study 2019 (GBD 2019) Disability Weights | GHDx (healthdata.org)) Finally, Aimmune wishes to point out that even if caregiver values are not accepted but all n=40 adolescent self-reported EQ-5D values are used to calculate the HSUVs for the entire population, i.e., not only the n=38 treatment-naïve adolescents from the online survey, but also the n=2 adolescents from the Palforzia treated survey, this would yield the following HSUVs, very similar to those used in Aimmune's base case. [redacted] **Index** **Mean (SE)** / **Difference** **Current HRQoL[1]** [redacted] **Up-dosing** [redacted] **Maintenance** [redacted] **Tolerate 6-8 peanuts[2]** [redacted] [1]Pre-trial for the N=2 treated; [2]Current HRQoL for the N=2 treated
Key issue 4: Resource use associated with anaphylactic reactions and adverse events	**NO**	Upon further review and consultation, Aimmune agrees with the ERG position that it is appropriate to assume an ambulance and A&E visit should be required for all anaphylactic reactions, regardless of the severity or whether caused by an accidental exposure to peanut or Palforzia treatment. Aimmune agrees therefore in the model that the same resource use assumed for accidental exposures to peanut requiring adrenaline should be applied to treatment-related anaphylactic reactions, regardless of severity, per the table below. Relatedly, Aimmune also agrees with the revised unit cost assumption proposed by the ERG for an ambulance call out (£257, based on reference cost ASS02, See and treat and convey).

Resource type	Resource use assumed per treatment-related anaphylactic reaction (all reactions regardless of severity)	Unit cost
Ambulance	100%	257
A&E visit	100%	168.00
Inpatient stay	10%	319.00
High Dose Antihistamine	100%	0.44
Adrenaline (1 single use)	100%	34.30
Total cost per event		**491.64**

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: ambulance cost	Section 1.6, page 10, paragraph 6 of the ERG report	NO	As stated above in the response to Key Issue 4, Aimmune agrees with the revised unit cost assumption proposed by the ERG for an ambulance call out (£257, based on reference cost ASS02, See and treat and convey).

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Issue 1 - Timing of food challenges including the timing at which utility gains are realised in clinical practice	The timing of treatment discontinuation and realisation of utility benefits are based on food challenges (2 for Palforzia, 1 for avoidance) conducted as part of the clinical trials.	The use of only one food challenge (at about 2 years) for Palforzia and none for avoidance was incorporated. Treatment costs were applied up until the food challenge (for all except those with a TRAE or accidental exposure) and utility benefits of known maximum tolerated dose (MTD) were realised only after the food challenge has been completed. Similarly, in the avoidance arm, utilities for MTD 300mg, 600mg and 1000mg are assumed to never be realised as no food challenge would be conducted.	This change has a small impact in the company's base case ICER: • Base case ICER: £21,581 • ICER after the change: £22,994
Issue 4 - Resource use associated with anaphylactic reactions and adverse events.	Resource use requirements for treating an anaphylactic reaction to Palforzia are lower than a patient who has an anaphylactic reaction due to accidental peanut exposure.	The assumption was made that all patients who require adrenaline due to an anaphylactic reaction would incur the same resource use (i.e., they would need an ambulance and transport to hospital, £491.64 per anaphylaxis event), regardless of whether the event was caused by treatment or by accidental exposure.	This change has a small impact in the company's base case ICER: • Original ICER: £21,581 • ICER after the change: £22,680

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Additional issue 1 – cost of ambulance (Section 1.6, page 10, paragraph 6 of the ERG report)	Ambulance cost £496.54 based on previous NHS Ambulance Services report and inflated to the current cost year using the consumer price index.	Changed as suggested by ERG to £257 (NHS reference cost for ambulance services: ASS02, See and treat and convey)	This change has a small impact in the company's base case ICER: • Base case ICER: £21,581 • ICER after the change: £21,452
Additional issue 2 – adding severe anaphylaxis reactions (Section 1.6, page 10, paragraph 4 of the ERG report and Scenario B3 in response to clarification questions)	Severe anaphylactic reactions were excluded due to rarity of events (one case reported in PALISADE, two cases in ARC004 daily dosing cohorts but later corrected to [redacted], [redacted] cases in ARTEMIS)	Severe anaphylactic reactions were included, even if occurrence was rare (as described in the Scenario B3 in response to clarification questions)	This change has a small impact in the company's base case ICER: • Base case ICER: £21,581 • ICER after the change: £21,743
Additional issue 3 – Including all moderate and severe TRAEs (Section 1.6, page 10, paragraph 4 of the ERG report and Scenario B4 in response to clarification questions)	Moderate and severe treatment related adverse events occurring in more than 5% of participants were included.	All moderate and severe TRAEs were included, even if occurrence was rare (as described in the Scenario B4 in response to clarification questions)	This change has a small impact in the company's base case ICER: • Base case ICER: £21,581 • ICER after the change: £21,684

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Company's preferred base case following technical engagement	Incremental QALYs: 0.862	Incremental costs: £20,458	After incorporating all changes, the ICER increased by 10% in comparison to the ICER presented in the original submission: • Base case ICER: £21,581 • ICER resulting from combining all the changes described: £23,745

NICE National Institute for Health and Care Excellence

New evidence supplement

Palforzia for treating peanut allergy [ID1282]

Proposed new evidence

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Proposed new evidence
Issue 3	**Alternative utility values – adolescents (n=40)**	Aimmune would like to present pooled data of all adolescent self-reported utility values (n=40, including N=38 treatment naive; N=2 Palforzia-treated).	Regarding utilities used in the cost-effectiveness model, the ERG prefers the use of adolescent self-reported data only. However, the ERG used data from n=38 treatment-naïve adolescents from the online survey, but did not include n=2 adolescents from the Palforzia-treated survey. Aimmune wishes to point out that even if caregiver values are not accepted but all n=40 adolescent self-reported EQ-5D values are used to calculate the HSUVs for the entire population, this would yield the following HSUVs, very similar to those used in Aimmune's base case. Pooled data of all adolescent self-reported utility values (n=40, including N=38 treatment naive; N=2 Palforzia-treated) are presented below.

[redacted]

	Index	
	Mean (SE)	Difference
Current HRQoL[1]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]
Tolerate 6-8 peanuts[2]	[redacted]	[redacted]

[1]Pre-trial for the N=2 treated; [2]Current HRQoL for the N=2 treated

Including these utility values will have small impact on the base case submitted ICER:

- Base case ICER: £21,581.
- ICER after all changes described in the technical engagement response form (company's preferred base case following technical engagement): £23,745.
- ICER after all changes described in the technical engagement response form with utilities for n=40 adolescents: £21,713.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Palforzia for treating peanut allergy [ID1282]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **20 September 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with peanut allergy and current treatment options	
About you	
1. Your name	**Mich Lajeunesse**
2. Name of organisation	**University Hospitals Southampton NHS Foundation Trust**
3. Job title or position	**Consultant in Paediatric Allergy & Immunology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with peanut allergy? ☐ a specialist in the clinical evidence base for peanut allergy or the technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for peanut allergy	
8. What is the main aim of treatment? (For example, to reduce the occurrence and severity of adverse reactions, to prevent anaphylaxis and reduce hospitalisations, to reduce stress and anxiety associated with peanut allergy.)	Aim of current treatment for peanut allergy is to reduce occurrence and severity of allergic reactions and improve quality of life, anxiety and activities of daily living. We provide information to safely avoid peanut containing foods and to provide child with a diet that it is as inclusive, varied and socially acceptable as possible, to reduce the impact of food allergy on activities of daily living whilst maintaining safety, to train family and the older child in the recognition of severe allergic reactions and the use of adrenaline autoinjectors.
9. What do you consider a clinically significant treatment	Reduction in severity of allergic reaction, prevention of anaphylaxis on consumption, increase in reaction threshold to beyond a point where accidental food contamination would cause symptoms.

response? (For example, reduce the occurrence of adverse reactions, prevent anaphylaxis, to no longer be allergic to peanuts.)	This is different from a total cure or sustained unresponsiveness which is the ultimate goal of treatment - able to eat peanut ad lib without reaction with variable and sometime prolonged gaps between consumption.
10. In your view, is there an unmet need for patients and healthcare professionals in peanut allergy?	Absolutely. Avoidance is not a treatment and there is no disease modifying treatment available.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Aim of current treatment for peanut allergy is to provide information to safely avoid peanut containing foods and to provide child with a diet that it is as inclusive, varied and socially acceptable as possible, to reduce the impact of food allergy on activities of daily living whilst maintaining safety, to train family and the older child in the recognition of severe allergic reactions and the use of adrenaline autoinjectors
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, Huber P, Luyt D, Till SJ, Venter C, Clark AT. Clin Exp Allergy. 2017 Jun;47(6):719-739. doi: 10.1111/cea.12957. PMID: 28836701 **NICE Food allergy in under 19s: assessment and diagnosis Clinical guideline [CG116] Published: 23 February 2011**

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Diagnostic pathway is well defined. Practice varies around provision of injectable adrenaline. Some provide AID to all peanut allergic patients other only to those with significant asthma or history of anaphylaxis to peanut. Practice also varies about dietary advice on avoidance of other nuts. Peanut allergy can be isolated where other nuts are tolerated or occur as part of a mixed nut allergy. Some with isolated peanut allergy avoid all nuts others eat tree nuts.
• What impact would the technology have on the current pathway of care?	Limited impact on the pathway of care as the diagnosis and avoidance advice is unaffected. Patients treated with Palforzia would have to carry adrenaline autoinjectors in the long term so this is also unaffected. There may be reduction in accidental reactions and anaphylaxis to food leading to reduced hospital admission. There may also be improvements in ability to eat food labelled may contain traces and other relaxation of strict avoidance lifestyle that may improve QOL of treated patients and their families.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Use of Palforzia will require considerable investment in paediatric allergy services.
• How does healthcare resource use differ between the technology and current care?	For peanut avoidance we see yearly before school age and then every 2-3 years after that in outpatients. Palforzia requires frequent repeat visits and prolonged observation during initial dosing and up dosing compared to current care. Maintenance treatment will require more frequent visits and monitoring than current avoidance.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Palforzia use should be reserved for specialist clinics experienced in the use of allergen immunotherapy and food challenges (as the food challenge setting is similar to the resources needed for Palforzia up dosing). There should be paediatric crash facilities on site in case of refractory anaphylaxis to up dosing.

	Once established this technology could be rolled out to larger secondary care services with dedicated paediatric allergy staff on site. This would be as part of a treatment network with the regional hub centre managing initial dose escalation and spoke centre managing routine up dosing and maintenance closer to home. Larger treatment networks will be required to provide treatment across all areas of the country in an equitable manner.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Centres with appropriate infrastructure – paeds crash team, paed allergy services, regular food challenge practice, allergen immunotherapy experience would require staff, space (eg paeds medical day ward) and training to run a Palforzia service.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Palforzia will provide disease modifying benefits that are a considerable advance on standard care.
• Do you expect the technology to increase length of life more than current care?	No, death from peanut allergy is very rare.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective: those with very low threshold reactors eg history of reaction to less than a peanut or food with may contain traces, those with a history of previous anaphylaxis to peanut, those with an isolated peanut allergy less effective those with multiple food allergies where Palforzia would only treat one of many food allergens those with severe or brittle asthma where treatment may be associated with more side effects those who are unable to manage regular home dosing due to lifestyle factors
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are many obstacles to the implementation of this treatment in current allergy services. Staff – additional medical and nursing staff to deliver care Time – significant increase in time required to deliver this treatment compared to current care including specialist out of hours cover to advise on home dosing Space – requires additional facilities within a suitable unit, where day ward space is already likely to be at a premium

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Monitoring allergy tests does not give an accurate estimate of desensitisation. Novel tests such as the Basophil Activation test might help but this is still experimental. Food challenge to establish reaction threshold is the gold standard. Food challenge is not required to deliver this service. Allergy clinics in the US and privately in the UK run oral immunotherapy services without providing supportive threshold challenges. I expect that the minority of patients will want an exit challenge to define reaction threshold. Whilst the start and maintenance of treatment is well defined the duration of treatment has not been fully established. Patients will be required to continue with dietary peanut on a regular basis ?daily ?weekly for life in order to maintain desensitisation. The timing of switch over the use of real world dietary peanut (such as M&M sweets) taken like medicine on a daily basis has not been established, but putatively could be considered after 2 years of stable maintenance on Palforzia. Some patients may continue to require the accurate dosing of Palforzia to maintain tolerance. The long term duration of this regular peanut consumption is not known. Other forms of allergen immunotherapy require 3-5 years of treatment before sustained unresponsiveness eg bee venom.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	Not all allergic reactions are the same from a psychological point of view. Allergic reactions around observed dosing are expected and will be managed by healthcare professional, reactions around dosing at home once again are expected and are likely to be recognised and treated promptly by parents.

the quality-adjusted life year (QALY) calculation?	This is different from allergic reaction for accidental exposure which are not expected, may be poorly recognised, with parent no present and Adrenaline not available. These unexpected allergic reactions have a greater impact on QOL than an expected reaction.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes and will be welcomed by peanut allergy sufferers.
• Does the use of the technology address any particular unmet need of the patient population?	It is the first disease modifying treatment available.
19. How do any side effects or adverse effects of the technology affect the management of the	Palforzia treated patient are more likely to suffer allergic reaction and anaphylaxis that those on an avoidance diet. However not allergy allergic reactions are the same. Reactions during up dosing are expected and occur in

condition and the patient's quality of life?	healthcare facility. There are improvements in quality of life with patient experiencing anaphylaxis during food challenge, are likely to be treated promptly by the family as such will be less severe. Chronic abdominal pain associated with dosing can be debilitating and is a cause of about 10% to stop treatment. Similarly there are lifestyle factors such as frequent travel to clinic, impact on school and social life, dosing on a full stomach and bans on exercise for hours after dosing that may treatment restrictive and not suitable for all families.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The UK clinical trials of Palforzia (ARTEMIS, ARC008) show that it is possible to deliver this in a UK setting. The trials required double blind food challenges at entry and exit as an extra layer of complexity that probably won't be used in clinical practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Severity of symptoms during accidental exposure to peanut / use of adrenaline / hospitalisation – measured but small numbers in trial Maintenance of tolerance following abstinence from oral peanut treatment – sustained unresponsiveness – not measured

	Safety and effectiveness of transition to dietary peanut following desensitisation – not measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Trials used surrogate of single tolerated dose of peanut at exit food challenge, which is a reasonable assumption as a surrogate, given the difficulty of collecting rare event data (accidental peanut exposure) in relatively short and small sample clinic trial. Single dose tolerance was part of a food challenge so the cumulative dose in the hours before the reaction was much higher.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Eosinophillic oesophagitis is a reported risk in oral allergen immunotherapy. There were no cases reported in clinical trials and I am not aware of this emerging in post licensure practice in the US. However it could be expected that this would occur in a minority of children receiving treatment.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for potential comparator treatment(s)?	Palforzia is the only licensed treatment available.

23. How do data on real-world experience compare with the trial data?	This is still relatively limited data from its post licensure use in the USA. We hope to develop a national evidence base at a UK wide scale using the BSACI registry for immunotherapy (BRIT).
Equality	
24. Are there any potential equality issues that should be taken into account when considering this treatment?	It is likely that Palforzia use will be led by the private sector in specialist clinics in the UK. This will allow UK private clinics to develop experience in its clinical use. This may help to develop a framework for service specifications for NHS services. Palforzia use should be limited by strict criteria based on clinical need. I am concerned that those in most need who are least able to pay will not have access to free NHS care for this treatment, as limited NHS capacity to provide Palforzia will be filled by the better informed and most vocal. Such access to services as dogged the NHS since its inception. The impact of equality and diversity on current access to allergen immunotherapy is being reviewed at a national level using BRIT registry data. The BRIT registry shows discrepancy in use of allergen immunotherapy in the devolved nations with no current patients in Scotland or Northern Ireland. Access to Palforzia in all devolved nations of the UK will be a challenge. Even in England there has been an unmet need for specialist allergy services for decades and it is unlikely that all regions would have access to specialist paediatric allergy services to lead on the development of services.

Topic-specific questions	
25. What are the psychological effects on people and their carers of living with a peanut allergy? How does this affect their day-to-day quality of life?	Food allergy has an impact on mental health similar to any chronic disease. In particular it could be considered to be like epilepsy in that there is risk of sudden onset acute illness that may be life-threatening. On another level it is like insulin dependent diabetes in that it is pervasive and requires constant vigilance. All food items have to be checked for their safety. Peanut allergy has a huge impact on quality of life and wellbeing. This can manifest in anxiety related to food and drink, children not eating outside of the family home, in rare instances not drinking at school or away from home either. Families adapt to manage depending on the perception of risk, which may include avoiding eating in restaurants, foreign holidays. We have employed a psychologist as part of our clinical team for several years.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
26. **Key issue 1:** Timing of food challenges including the timing at which utility gains are realised in clinical practice **Questions:** Are people on peanut avoidance diet currently being offered food challenge in NHS practice? How many food challenges do you anticipate would be offered	**Questions:** Are people on peanut avoidance diet currently being offered food challenge in NHS practice? Food challenges are offered to children for diagnosis of peanut allergy (rare) as allergy tests most often can make a diagnosis with a good clinical history. They are also used to try to prevent onset of peanut allergy in infants with borderline allergy tests results as per prevention strategy described in the LEAP study. Most commonly challenges are used to test tolerance and show resolution of symptoms following improvement in allergy tests. Occasionally a demonstration challenge will be offered to a teenager with peanut allergy who does not remember having an allergic reaction (as it occurred when they were an infant). This can help with anxiety if managed by a specialist team, but is also associated with a risk of anaphylaxis. Food challenges are not currently used to define reaction thresholds in clinical practice which is what would be required for Palforzia. **Q: How many food challenges do you anticipate would be offered to people having treatment with Palforzia in the NHS, and how long after starting the therapy?**

to people having treatment with Palforzia in the NHS, and how long after starting the therapy? Do you think people taking Palforzia (and/or their carers) would feel any positive impact of treatment on their quality of life before knowing the results of the food challenge, or only after it?	Although food challenges were used as end points in the clinical trail the are not necessary for clinical practice. If used at all a single challenge at exit should suffice. **Q: Do you think people taking Palforzia (and/or their carers) would feel any positive impact of treatment on their quality of life before knowing the results of the food challenge, or only after it?** Food challenges can be helpful to demonstrate this, but equally change to dietary peanut may act as a surrogate for threshold challenge.
27. **Key issue 2:** Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance. **Questions:** In your opinion, what proportion of people (and/or their carers) would	**Questions:** In your opinion, what proportion of people (and/or their carers) would accept stopping treatment after 2 years (and a food challenge) and switching to regularly including peanuts in their diet? What concerns might people have when making this decision? I expect that the majority of patient would accept change to dietary peanut after 24 months with or without food challenge. This is because such a change would further reduce the burden of treatment and frequency of clinic visits. There will be a minority for whom Palforzia will remain the long term preference ether because of anxiety (where an exit challenge may be useful to define threshold) or because of borderline tolerance to the 300mg dosing where continued accurate dosing at maintenance would be important.

accept stopping treatment after 2 years (and a food challenge) and switching to regularly including peanuts in their diet? What concerns might people have when making this decision? Do you think people who are able to include peanuts in their diet following treatment would continue to regularly eat peanuts or peanut-containing foods in the long-term? What proportion may switch back to avoiding peanuts in their diet, and how long after starting including peanuts in their diet? What are the main concerns that might stop people from	Do you think people who are able to include peanuts in their diet following treatment would continue to regularly eat peanuts or peanut-containing foods in the long-term? What proportion may switch back to avoiding peanuts in their diet, and how long after starting including peanuts in their diet? I think that the majority will continue to include peanut especially of the frequency could be weaned off from daily to once or twice weekly after a few years. I would suggest that 1/10 may stop real world treatment after a few years. How dietary peanut is used and explained by physicians may impact on patient perceptions – for instance if it is described as “dietary peanut” does not sound as important or necessary as “Real World Immunotherapy”. **Q: What are the main concerns that might stop people from continuing to regularly eat peanuts after treatment?** Ongoing aversion to peanut despite desensitisation Restrictions around meals and exercise after dosing

continuing to regularly eat peanuts after treatment?	
28. **Key issue 3:** Patient health state utility values **Questions:** Do you think assessment of health-related quality of life could differ depending on whether patients themselves (adolescents) or carers (children) complete it? If yes, in what way? Do you think assessment of health-related quality of life by parents or carers of children with peanut allergy could be capturing the impact of peanut allergy on their own quality of	**Questions:** Do you think assessment of health-related quality of life could differ depending on whether patients themselves (adolescents) or carers (children) complete it? If yes, in what way? I think that many adolescents are shielded from the full impact of their disease by their parents. They will often have been raised in a socially restricted way in order to protect them, and will be less able to say how FA impacts of their quality of life and expectations. Thus, they may underestimate the impact of FA on their QOL as they have been cocooned from the difficulties of independent living. **Q: Do you think assessment of health-related quality of life by parents or carers of children with peanut allergy could be capturing the impact of peanut allergy on their own quality of life, rather than on the quality of life of their children?** I am sure that there will be an element of both parental QOL and proxy child QOL in parent reporting.

life, rather than on the quality of life of their children?	
29. **Key issue 4:** Resource use associated with anaphylactic reactions and adverse events. **Questions:** Would you expect the management (and therefore associated resource use) of severe anaphylactic reactions requiring adrenaline to differ depending on whether it was caused by accidental peanut exposure, or by treatment with Palforzia? Do you think that the severe but rare treatment-related adverse events may have impact on health-related	**Questions:** Would you expect the management (and therefore associated resource use) of severe anaphylactic reactions requiring adrenaline to differ depending on whether it was caused by accidental peanut exposure, or by treatment with Palforzia? All Palforzia treated patients would be expected to use adrenaline promptly and contact emergency services for severe anaphylactic reactions. The expectation is that they would be observed in A&E. However in practice many anaphylactic episodes are not taken to hospital even after adrenaline has been given as first aid. I think that this is because paramedics are better trained and have better communication with senior clinicians in emergency departments that reduces the need for transfer in. Palforzia reactions are more likely to occur around dosing and be expected events rather than accidental exposure. They are more likely to receive adrenaline early and less likely to be severe compared to not treated patients as parents are trained and expectant. Because of these factors I think that it is reasonable to assume that Palforzia treated patients will be less severe and less likely to attend emergency department or require admission for severe allergic reactions. **Q: Do you think that the severe but rare treatment-related adverse events may have impact on health-related quality of life and/or costs, and therefore should be included in the economic model?** Yes. Severe events will have an impact on HRQOL

quality of life and/or costs, and therefore should be included in the economic model?	
30. Additional questions: How is peanut allergy currently being diagnosed? Would you expect any additional testing would be needed to assess suitability for treatment with Palforzia?	Peanut allergy is diagnosed from suggestive clinical history and confirmed by evidence of allergic sensitisation by skin prick test or specific IgE. Where there is a history of comorbid pollen food syndrome checking peanut component IgE (Ara h2 / Ara h8) can be helpful to ensure that severity of peanut allergy has been assessed. If this initial diagnostic process is undertaken with care then no further testing should be required before starting treatment. However if it has been some years since testing repeat testing before starting Palforzia would be advised to ensure that natural tolerance has not been acquired.
31. Are there any important issues that have been missed in ERG report?	Not all allergic reactions are psychologically the same. There is a big difference between an expected allergic reaction following dosing either in hospital or at home and one occurring away from home by accident. The later has a bigger impact on QOL. The former may even reduce anxiety and improve QOL if handled well by healthcare professionals.
PART 3 -Key messages	
31. In up to 5 sentences, please summarise the key messages of your statement: • Palforzia is the first disease modifying treatment for peanut allergy and will be welcomed by families of peanut allergic children	

- Although it increases allergic reaction and use of adrenaline not all reactions have same impact on mental health and QOL. Expected reactions may even improve wellbeing if handled well.
- Its use will be in addition to standard care pathways but does not need to include food challenges as a standard exit procedure
- People experiencing anaphylaxis in the community are not always admitted to hospital despite guidelines to contrary. Mild episodes and those treated promptly with adrenaline are less likely to require admission.
- There are equity and diversity issues that should be addressed to provide nationwide access to this treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Palforzia for treating peanut allergy [ID1282]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **20 September 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with peanut allergy and current treatment options	
About you	
1. Your name	**Professor Adam Fox**
2. Name of organisation	**Guy's & St Thomas' Hospitals NHS Foundation Trust**
3. Job title or position	**Consultant Paediatric Allergist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with peanut allergy? ☐ a specialist in the clinical evidence base for peanut allergy or the technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have no links to the tobacco industry. I have completed consultancy work for Aimmune in relation to Palforzia on behalf of GST Consulting (the consulting arm of my NHS organisation) for which I do not receive a personal fee. I has also been a co-investigator of clinical trials for both Aimmune and DBV. I am President of the BSACI, member of NASG and Chair of the Health Advisory Board fo Allergy UK and all 3 organisations have received sponsorship from Aimmune/DBV. I am a director of Food Allergy Immunotherapy ltd which will likely offer Palforzia treatment to patients on a private basis.**
The aim of treatment for peanut allergy	
8. What is the main aim of treatment? (For example, to reduce the occurrence and severity of adverse reactions, to prevent anaphylaxis and reduce hospitalisations, to reduce stress and anxiety associated with peanut allergy.)	There are 3 main aims - To increase the threshold at which a patient reacts to peanut - To reduce the severity of reactions that occur - To reduce anxiety/improve quality of life in relation to the risk of severe reactions through 1 &2 above Currently, management is passive ie avoidance with training to manage accidental exposures whereas this represents a more active treatment modality, in the context of complete avoidance being challenging.
9. What do you consider a clinically significant treatment	This is a challenging question and there may be a different answer for different patients as they have very different expectations. In my practice, most patients will report that protection from small exposures would still be significant for them and achieving a maintenance dose of 300mg, thought to offer 'bite-protection' from small accidental

response? (For example, reduce the occurrence of adverse reactions, prevent anaphylaxis, to no longer be allergic to peanuts.)	exposures would still be a worthwhile endeavour. Achieving a level of tolerance to 1000mg would very reasonably be considered highly clinically significant in terms of day to day peanut avoidance. However, it remains unclear, without longer term, post-marketing surveillance, how much of a real impact this may have although if it meaningfully improves patient's quality of life by reducing their anxiety regarding such exposures, then this would be a significant outcome in itself. The lack of long term 'sustained unresponsiveness' remains a concern with the requirement for long term continuation of treatment necessary to maintain the effect.
10. In your view, is there an unmet need for patients and healthcare professionals in peanut allergy?	I strongly believe there is. Almost all patients I see raise the issue of OIT and almost invariably positive. They find the passive approach of simple avoidance deeply frustrating and commonly report anxiety in relation to small exposures, which would be avoided through successful OIT. Likewise, physicians find managing patients' anxiety in relation to very small exposures difficult as whilst severe reactions are very rare, reactions are wholly unpredictable making reassurance difficult.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	By avoidance ideally supported by dietetic advice (eg relating to reading allergen labels), training to identify and manage allergic reactions, and follow up to look for tolerance and the presence of co-morbidities eg asthma. This is essentially a passive process.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are guidelines eg NICE CG116 which relates to assessment and diagnosis, and both generic Food Allergy & Anaphylaxis guidelines from EAACI (2014) and more specific BSACI guideline for Diagnosis and Management of Peanut & Treenut allergy (2017). However, as the 'treatment' is relatively straightforward and standardised ie 'avoid' you hear little reference to these guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – whilst there will inevitably be some local differences, pathways are broadly consistent ie diagnose, avoid, follow up. There is an RCPCH National Care Pathway for food allergy which defines this pathway and all services I am aware of broadly adhere to this. There are small pockets of practice where OIT will be offered to small, select groups of patients using personalised protocols using native peanut but none on a large scale that I am aware of although EAACI guidelines do state that OIT is an option. One centre in Cambridge is offering peanut OIT privately (Camallergy) and I have started to use a Canadian published protocol for children under 5 using Bamba snacks.

• What impact would the technology have on the current pathway of care?	This would be a paradigm shift for allergy services as this would be the first OIT treatment for most. It would have major implications on - Care pathways - Infrastructure - Staffing - Operating costs - Capacity Most food allergy clinics are essentially structured as diagnostic services ie securing a diagnosis, advising avoidance and then following patients up sometimes only years later. Introduction of Palforzia, or indeed any OIT programme structured in a similar way will have profound implications on how the service would be delivered and this will require investment of money, time and energy. There remains debate/controversy around how OIT programmes should look and whether a standardised capsules is required for anything beyond the smaller doses (which are hard to measure otherwise) but the real cost of delivery would be in finding the additional space and staff to safely offer the treatments. However, as OIT is becoming a reality, this needs to happen as I strongly expect treatments to other allergens will follow.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – as detailed above, delivery requires a step change in service delivery with patients who previously would have simply had annual outpatient follow up, requiring a large number of daycase visits with ongoing access to advice to support them.
• How does healthcare resource use differ between the technology and current care?	Provision for current management is minimal ie generic outpatient with very occasional access to daycase facilities for any diagnostic uncertainty either when diagnosis is first suspected or if there is a chance allergy has been outgrown. Delivery of Palforzia treatment requires multiple day case visits in the short term, access to ongoing advice and then ongoing follow up.
• In what clinical setting should the technology be used? (For example,	I strongly feel this should start in specialist clinics with experience of managing higher risk day case activity ie where anaphylaxis can be managed safely, given the risks of the treatment. The UK and US (where this treatment will be primarily used) have very different structures, with many US allergists working outside of a hospital setting but it teams with other allergy staff where there is always access to staff and equipment experienced in managing allergy

primary or secondary care, specialist clinics.)	emergencies. In the UK, this type of setting rarely exists outside of the acute hospital setting and hence this should start in the more specialist setting, which could still include DGHs where there is experience at carrying out oral food challenges.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This will vary according to the service but if we limit provision initially to services that already offer oral food challenges, then the infrastructure/staff should already be in place but very likely with nothing like the capacity required eg Some may not have the bed capacity to manage OIT visits on top of existing food challenge demand and hence require additional space as well as additional staffing. There also needs to be enough staff capacity to ensure patients can always receive advice, including out of hours, regarding dose changes.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes for those able to achieve maintenance dose
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – I believe it will where it is successful and I believe patients feel this very strongly too. I am not sure this has really be adequately captured in the studies but likewise remain uncertain how much of the enhanced quality of life may come from regular contact and access to specialists. Most patients I meet before discussing OIT as an option have very little understanding of the really risk of severe reactions, strategies for managing 'may contain' labels or a clear sense of how to identify and manage allergic reactions. Ideally studies into the impact of palforzia or other OIT need to compare QoL with these fully addressed in both groups. That said, my personal view is that the QoL of life gains would still be meaningful.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some groups would benefit less eg those reacting to peanut due to Pollen-Food syndrome ie due to PR10 cross sensitisation, those who are very sensitive and thus react to very low dose or have had very severe reactions in the past (making the risk of regular exposure too great). It may also be less relevant for those already able to tolerant larger amounts even without treatment although these would be very difficult to define given the impact of co-factors on their eliciting dose. I suspect those patients with severely impaired QoL due to anxiety may gain the most from knowing their threshold for reactivity is higher but I would be very reticent to suggest this as a method for rationing treatment as it would simply incentivise patients to overstate their impairment. There may also be issue with patients less able to manage treatment ie those from more chaotic households, lower SEGs or where there may be language/communication issues where this may represent an increased clinic riks and decreased likelihood of treatment success and/or ongoing compliance with therapy.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Unequivocally, this will be harder both for patients and HCPs. Patients – need for regular up dosing visits and the need to manage daily exposure, fitting this into their daily lives, together with the additional risk of reactions to the OIT itself. HCPs – as detailed above, a step-change in the nature of the provision for patients on treatment.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A definitive diagnosis will be needed to initiate treatment – different services will define this based on their capacity ie some may not require a food challenge if there is a recent reaction and clear positive tests although some may offer incremental challenges to establish eliciting doses, especially if they have to ration treatment and may only offer those whose react below a certain threshold. Treatment would stop if patient is no longer compliant (parameters would need to be set) or has a severe reaction. I also suspect services will start to 'bespoke' the way they use palforzia, most likely to reduce the cost ie once doses above 100mg have been reached, it is easier to measure out native peanut in a reliable way, negating the need for Palforzia and services may move to native peanut at varying points in treatment. Once maintenance dose of 300mg has been achieved this is particularly likely.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	HRQL do not apply particularly well to allergy in my opinion and there is room for the use of better tailored measures of QoL, which would also need to be applied over a longer term of follow up to really understand their impact.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes but only in the sense that all OIT is innovative. Packaging of peanut into capsules seems to be a detail rather than the innovation itself however, if this is what makes the delivery of peanut OIT safe and accessible then yes, for some patients, this will provide important clinical benefit but as outlined above, how much of that comes from Palforzia and how much from native peanut OIT will no doubt vary.

• Is the technology a 'step-change' in the management of the condition?	Yes – as detailed above but important to recognise that this treatment will not be suitable for all patients or the standard of care but instead an important option available for those who, following a detailed period of shared decision making, wish to progress.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, for those where the anxiety of small accidental exposures is having a major impact in QoL and are able to understand the risk-benefit balance of the treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is a fundamental trade off in any OIT programme, with Palforzia being no exception, between the risk of reacting to the treatment itself being balanced with he reduction in risk of subsequent reactions. This was highlighted in the PACE study (Chu et al Lancet 2019) showing that the risk of anaphylaxis was greater with peanut OIT than with avoidance but this did not account for the setting of the reaction ie a reaction in a controlled/expectant medically supervised or home setting versus unexpected reactions. Patients I discuss this with fully understand this and remain keen on treatment so I think its reasonable to assume the impact would not be adverse…until it does become so in which cases patients must be repeatedly reminded that they are not obliged to continue treatment.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes in the sense that they compare treatment to avoidance, which is the current UK standard.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Safety, effectiveness and QoL.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	It is well known that many patients dislike eating peanut and it is unclear what the long term effect will be especially when younger children, who are directed to consume the food by their parents as they believe it is in their best interests, become older and most independent/able to resist their parents demands. There will be mitigating strategies but work is required to confirm that this will be an effective long-term treatment.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I think there is a still a gap around long term adherence as detailed above.
22. Are you aware of any new evidence for potential comparator treatment(s)?	Emerging data around epicutanoeus immunotherapy and increasing experience of peanut OIT in younger children in clinical practice eg Soller et al JACI 2021

23. How do data on real-world experience compare with the trial data?	From discussing with US colleagues using Palforzia, experiences relating to safety and efficacy do seem to be in line with expectations from the studies.
Equality	
24. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes – this is a real concern as this treatment must only be offered by competent services and these are not equally distributed across the UK, reflecting a known inequity of service provision. There are large areas eg Scotland, the South West, with very minimal service provision meaning that access in these areas will be much harder. As with other specialist services, with a complex treatment regime with multiple visits I believe there is a risk of disadvantage to patients where travel is more challenging, parents are working multiple jobs or on unpredictable hours and where there may be language issues. I have long standing concerns, detailed in an editorial, about existing inequities, resulting in 'first class' and second class' allergy citizens and this may widen the gap further. (Fox AT, Turner P, Ewan PW. Towards excellence in paediatric allergy care for all. *Clin Exp Allergy*. 2019 Mar;49(3):266-268.)
Topic-specific questions	
25. What are the psychological effects on people and their carers of living with a peanut allergy?	I would endorse the responses to this question by the 2 patient groups – the psychological impact is highly significant in terms of the pervasive anxiety that impacts the whole family. However, I would also add the often missed impact

How does this affect their day-to-day quality of life?	that having a severe but non- fatal reaction can have, with more recent evidence suggesting this can shade into the area of PTSD. Chung MC, Walsh A, Dennis I. Trauma exposure characteristics, past traumatic life events, coping strategies, posttraumatic stress disorder, and psychiatric comorbidity among people with anaphylactic shock experience. Compr Psychiatry. 2011;52(4):394-404. Lee Y, Chang HY, Kim SH, Yang MS, Koh YI, Kang HR, et al. A Prospective Observation of Psychological Distress in Patients With Anaphylaxis. Allergy Asthma Immunol Res. 2020 May;12(3):496-506. doi:10.4168/aair.2020.12.3.496

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
26. **Key issue 1:** Timing of food challenges including the timing at which utility gains are realised in clinical practice **Questions:** Are people on peanut avoidance diet currently being offered food challenge in NHS practice? How many food challenges do you anticipate would be offered	Peanut allergic patients avoiding peanut are only offered food challenges if there is clear evidence on follow up testing (Skin and blood test) that they may have outgrown their allergy. This is very rare over 4 years of age and there is no place at all in regular NHS practice for routine food challenges in this context otherwise. Palforzia will place NHS services under specific pressure for day case beds, where updosing and food challenges are likely to occur and this will have to be balanced with the needs of other patients needing diagnostic food challenges. This means there will be real pressure to minimise the number of challenges and I would anticipate a maximum of one (and even a case being made for none!). This could be anytime from 1-2 years after attaining maintenance and may depend more on logistical factors of bed space that anything else. I anticipate patients, based on successful completion of updosing (and based on the side effect profile they had) may well feel some of the additional benefit based on the published data that their tolerance increases despite remaining on 300mg, even prior to challenge but this would be very difficult to quantify.

to people having treatment with Palforzia in the NHS, and how long after starting the therapy? Do you think people taking Palforzia (and/or their carers) would feel any positive impact of treatment on their quality of life before knowing the results of the food challenge, or only after it?	
27. **Key issue 2:** Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance. **Questions:** In your opinion, what proportion of people (and/or their carers) would	The assumptions that approx. 30% of patients who transition to peanut would drop out in the subsequent 2 years feels reasonable and there is little in terms of data to inform this (hence the need for the SHELF process). However, this would be very influenced by certain factors eg the level of motivation of the families at the outset, the side effect experiences during updosing and maintenance and the level of support from the service eg dieticians, at making the peanut more palatable. I am less convinced by the 17% remaining on palforzia – I cannot see NHS services being able to justify offering this, given the cost, when there is a 'free' alternative in the form of native peanut. Whilst there may be an occasional case of exceptional circumstances, I simply cannot see ongoing use of palforzia being sustainable for the NHS service especially as it will likely mean other patients not being offered. If it came down to refusing an ongoing supply (but hopefully offering dietetic and even psychological support) I suspect most would move to native peanut.

accept stopping treatment after 2 years (and a food challenge) and switching to regularly including peanuts in their diet? What concerns might people have when making this decision? Do you think people who are able to include peanuts in their diet following treatment would continue to regularly eat peanuts or peanut-containing foods in the long-term? What proportion may switch back to avoiding peanuts in their diet, and how long after starting including peanuts in their diet? What are the main concerns that might stop people from	I anticipate the key reason for stopping treatment with regular peanut would either be adverse reactions eg with a viral infection, or the child being taste averse. This will be age dependent as children become more independent and able to resist parental demand to consume the food but I am comfortable with the SHELF estimate and have no compelling reason to disagree.

continuing to regularly eat peanuts after treatment?	
28. **Key issue 3:** Patient health state utility values **Questions:** Do you think assessment of health-related quality of life could differ depending on whether patients themselves (adolescents) or carers (children) complete it? If yes, in what way? Do you think assessment of health-related quality of life by parents or carers of children with peanut allergy could be capturing the impact of peanut allergy on their own quality of	There is little evidence I am aware of to inform this from other areas of allergy, but from assessment of the impact of treatment for allergic rhinitis, this same disparity between personal and parental estimation of QoL has been seen. In this case, the effectiveness of the medication was underestimated by parents relative to children's own assessment and the effect size of the intervention appeared to increase, the more the reliance on the child's own reporting. I am unaware of data relating to such disparity outside of the allergy field but this does highlight the need for child friendly methods of assessing QoL. There does feel an inevitability that parents will take a more holistic, family focussed and future facing view of QoL whereas the child will be only able to focus on the impact on their own world, in the present. It likewise feels likely that different personal 'value' assigned by child or parent to different aspects of how QoL are assessed will mean that there will always be some shortcomings in parent assessments. That said, the QoL impact of a treatment on other family still has a potential benefit that should also be considered and that in turn will also impact on the child regardless of the direct impact on them. Berger B, Amar N, Tarpay M, Van Bavel J, Muraro A, Wickman M, Juste J, **Fox AT**, Nieto A, Valovirta E, Meltzer E, Bousquet J. Efficacy of MP-AzeFlu in children with seasonal allergic rhinitis: importance of paediatric symptom assessment. *Pediatr Allergy Immunol* 2016;27(2):126-33.

life, rather than on the quality of life of their children?	
29. **Key issue 4:** Resource use associated with anaphylactic reactions and adverse events. **Questions:** Would you expect the management (and therefore associated resource use) of severe anaphylactic reactions requiring adrenaline to differ depending on whether it was caused by accidental peanut exposure, or by treatment with Palforzia? Do you think that the severe but rare treatment-related adverse events may have impact on health-related	Whilst I understand the reasoning behind assigning the same management, in practice I would not expect this to be the case although the reasons work in opposite directions so may simply counteract each other. Whilst patient should be trained to recognise anaphylaxis and are expected to use the AAI and then call an ambulance, in practice this all happens much less commonly than expected. 1) Most patients do not recognise anaphylaxis when it occurs and thus do not use adrenaline and do not call an ambulance. As most cases self-resolve, there is usually less healthcare utilisation than expected. In Noimark et al, Clinical Experimental Allergy 2012, 969 patients reported 466 reactions in the previous year. 245 of these reactions were anaphylaxis but an AAI was used in only 41 (16.7%). The most common reason cited for not using AAI was that it wasn't felt necessary. I strongly suspect that patients on Palforzia, who would have received additional training on anaphylaxis, are actively encourage to aggressively treat any reactions and are actively observing their child after peanut exposure are all factors that would make them more likely to recognise anaphylaxis and treat it appropriately with AAI. This would thus increase the likelihood of a Palforzia anaphylaxis leading to use of an AAI. 2) From experience, one of the key drivers for calling an ambulance is not only fear of the reaction but a fear and reticence to use an AAI. Many patients will call ambulances for minor reactions (especially in younger children) and often, will do so without using the AAI that they have and have been trained to use or they simply don't have it with them or don't feel confident to use it correctly. This, I believe, is exacerbated by a reaction being somewhere the patient's carer feels they are not in control eg unfamiliar environments or unsure how close by help may be. When reactions occur to Palforzia, they are in a highly managed environment either under medical supervision or at home, with the medication they need very much available. In this latter setting, given that most anaphylaxis is mild in nature, I strongly suspect patients will feel more comfortable to give their AAI and despite direction otherwise, will do so and observe, without calling an ambulance.

quality of life and/or costs, and therefore should be included in the economic model?	The two issues above will be impossible to quantify without prospective research and may well counteract each other overall and negate their effects but the parity of cost of management of these different contexts of reactions is a significant assumption.
30. Additional questions: How is peanut allergy currently being diagnosed? Would you expect any additional testing would be needed to assess suitability for treatment with Palforzia?	Diagnosis involves (based on NICE CG116) i) Clinical history ii) Confirmatory testing (skin prick, IgE inc component blood testing and emerging BAT) iii) Oral food challenge for diagnostic uncertainty In reality, most diagnosis only reasonably require i & ii although access to palforzia may only be an option when it is some years since the child has reacted and without highly positives tests, a challenge may be preferred (and further justified to screen out those only reacting to higher doses of peanut already). Ideally, patients should only be avoiding peanut if the clinician is highly confident that they are allergic – the same expectation if they were to start Palforzia.
31. Are there any important issues that have been missed in ERG report?	no
PART 3 -Key messages	
31. In up to 5 sentences, please summarise the key messages of your statement: • Peanut OIT is a paradigm shift in the management of food allergy and likely a signal of more profound change in the management of food allergy as a whole	

- Palforzia is one approach to peanut OIT and may well be modified and used variably in different places according to capacity and infrastructure of the services
- Delivery of Palforzia will require signficanct change in clinical pathway and service delivery which will require investment
- For the right patients, Palforzia can make a significant difference in quality of life but significant efforts around shared decision making will be needed to get this right
- Long term compliance with treatment and long term impact on QoL remains unclear and will require ongoing monitoring to better understand

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Palforzia for treating peanut allergy [ID1282]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **20 September 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with peanut allergy and current treatment options	
About you	
1.Your name	**Sarah Baker and Hannah Bell**
2. Are you (please tick all that apply):	☐ a patient with peanut allergy? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with peanut allergy? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Anaphylaxis Campaign
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Patient feedback via our helpline service, support groups and members. Our members include individuals and families living with severe allergies and at risk of anaphylaxis as well as healthcare professionals working within the speciality of allergy. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is it like to live with peanut allergy? What do carers experience when caring for someone with the condition?	Living with or caring for someone with severe allergies has implications for many different areas of daily living including :- **Shopping and Preparing Food –** • extra time reading labels • extra cost for free-from foods • recipes can change so need to check labels with every purchase • understanding the meaning of 'may contain' labels on packaging • avoiding cross contamination in the kitchen • extra time cooking from scratch • weaning an infant with allergies – how and when? **Eating Out –**

	• Some foods seen as too high risk e.g. Asian food & nuts • extra communication needed with restaurant • lack of awareness in staff of allergy issues • lack of options on menu – reduced choice • risk of cross contamination • buffets problematic – high risk of cross-contamination • difficult socially or at work with catered events and shared kitchens– social exclusion • having to carry adrenaline everywhere – must carry medication at all times **Travelling –** • Flying can be stressful – enclosed air space - difficult to avoid allergen • Airline may not be accommodating e.g. serving allergen to other travellers in confined spaces • have to have GP letter to carry adrenaline on plane • difficulties communicating allergy in foreign language • hard to get adequate travel insurance • may have to pack 'safe' foods for emergencies **Seasonal Events –** • often heavily based around foods e.g. chocolate at Easter, nuts at Christmas • Family members may lack understanding and prepare unsafe food or gifts • Pressure to consume religious or cultural foods that are unsafe **Young People –** • Young people between 16-24 years old are frequently recognised as being most at risk of anaphylaxis. • Decrease in parental support – leaving home for the first-time managing allergy independently • More risk taking – experimenting with new foods, travelling alone, alcohol potentially affecting decisions • Reluctance to carry adrenaline auto-injectors and to tell peers about their allergies

	Education – Parents have to consider - • Choosing a school for a child with severe allergy – is the school 'Allergy aware'? • Putting in place an individual healthcare plan for the child • Does the school hold 'spare' adrenaline auto-injectors in line with government guidance? • Have the staff had allergy and anaphylaxis first aid training? • Will the child have access at all times to their own two adrenaline auto-injectors? • Does the school undertake an annual allergy risk assessment? • Does the school have policies for children with medical conditions including allergies? • Are the catering facilities allergy aware and inclusive?
Current treatment of the condition in the NHS	
7. What do patients or carers think of the current treatments and care available for peanut allergy on the NHS?	The only current way to manage severe allergy is complete avoidance of the allergen and carrying two adrenaline auto-injectors as emergency treatment in case of accidental exposure. **Patients/Carers report -** • Lack of understanding in primary care - appropriate referral, treatment, support and education • Can be a long wait to see a specialist and get a diagnosis or follow-up • uncertainty about when to use medication • confusion about how many adrenaline auto injectors to carry

	• understanding how and when to use adrenaline auto injectors • concerns about setting up a care plan – care and safety at school • lack of appropriate NHS followup following emergency treatment for anaphylaxis (in line with NICE CG134)
8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need. There are currently no effective treatments available on the NHS to reduce the severity of an allergic reaction from accidental peanut exposure. The development of AR101 is widely and eagerly anticipated by families with children who may be eligible for the treatment.
Advantages of this treatment	
9. What do patients or carers think are the advantages of the technology?	Patients/Carers report that they believe this treatment will - • reduce the burden of managing all of the implications of living with a severe allergy outlined in section 6 above due to decreased risk of a severe allergic reaction. • Reduce the psychological burden of living with anaphylaxis as outlined in section 14 below.
Disadvantages of this treatment	
10. What do patients or carers think are the disadvantages of the technology?	Patients/carers report concerns about - • Burden of maintaining the schedule of daily treatment • Risk of side effects – potential for mild, moderate or severe allergic reactions • Burden of monitoring child for side effects • Psychological effect on child if side effects experienced • Psychological issues around consuming allergen previously strictly avoided.

	Concerns about longevity of results following conclusion of treatment
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	With young people between 16-24 years old recognised as being most at risk of anaphylaxis, there may be an argument for prioritising treatment for the older end of the suggested treatment range of 4-17 years in order to offer the most protection to those most at risk.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	All eligible families should have equal opportunity to access the technology with patient information available in a variety of accessible formats to cater for a diverse range of needs.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Consider that treatment will likely reduce the number of severe allergic reactions as a result of accidental exposure, thus reducing need for hospital admissions and costly emergency care.
14. What are the psychological effects of living with a peanut allergy? How does this affect your day-to-day quality of life?	Living at risk of anaphylaxis can cause extreme anxiety – especially if the cause is unknown or it is a difficult allergen to avoid. Experiencing anaphylaxis is often very traumatic and individuals can become so anxious they find it hard to tell the difference between a severe allergic reaction and a panic attack. Quality of Life - • **Infant –** issues around weaning – what and when, childcare issues – ensuring safety and awareness with third party caregivers and

	relatives such as grandparents/parental anxiety and trauma-anaphylaxis is a life threating condition • **School Age child –** Ensuring safety at school - Allergy Action plans/spare pens in schools/staff training and awareness/risk assessment/bullying due to allergy/parental anxiety/ having to 'let go' • **Adolescent –** Increased risk-taking behaviour/denial – not wanting to be different/embarrassed to ask questions eating out/ reluctance to carry AAIs/parental issues with letting go – transfer of responsibility for managing the allergy **Adults –** May be issues at work securing reasonable adjustments (severe allergy CAN be considered a disability for the purpose of the Equality Act though little actual precedence) Young adults still at increased risk of severe reaction for reasons outlined under adolescence/ can be more difficult to access adult allergy services – often not reviewed for many years/

PART 2 – Technical engagement questions for patient experts

Issues arising from technical engagement

We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

15. **Key issue 1:** Timing of food challenges including the timing at which utility gains are realised in clinical practice **Questions:** Are people on peanut avoidance diet currently being offered food challenge in NHS practice? How many food challenges do you anticipate would be offered to people having treatment with Palforzia in the NHS, and how long after starting the therapy? Do you think people taking Palforzia (and/or their carers) would feel any positive impact of treatment on their quality of life before knowing the results of the food challenge, or only after it?	The suggestion of offering only one food challenge at 2 years post treatment initiation may be very difficult for patients to maintain motivation without any testing to evaluate effectiveness. Food challenge at 1 year post treatment initiation may be more realistic. Older teenagers will be moving through milestones such as starting secondary school, university etc and will likely want to know their allergy status to help them manage their allergy risk in new environments. Anaphylaxis Campaign feels that QOL benefits of improved peanut tolerance CAN be realised prior to food challenge – increasing tolerance could reduce severity of reactions to accidental exposures whether the patient is aware of their current tolerance level or not and awareness of this possibility may provide some relief from health related stress and anxiety.
16. **Key issue 2:** Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance. **Questions:** In your opinion, what proportion of people (and/or their carers) would accept stopping treatment after 2 years (and a food challenge) and switching to regularly	The proportion of people and their carer's more likely to accept stopping treatment and transitioning to peanuts in the diet after 2 years (and a food challenge) is likely to be higher for those who reached treatment doses of 2000mg as opposed to those at the lower doses of 300mg, 600mg and 1000mg. Those young people aged 17 years and over would potentially be more likely to have peanuts in their diet to avoid "being different to their friends", they are bigger risk takers and are more likely to be away from parental controls regarding diet.

including peanuts in their diet? What concerns might people have when making this decision? Do you think people who are able to include peanuts in their diet following treatment would continue to regularly eat peanuts or peanut-containing foods in the long-term? What proportion may switch back to avoiding peanuts in their diet, and how long after starting including peanuts in their diet? What are the main concerns that might stop people from continuing to regularly eat peanuts after treatment?	In addition, young people who have committed to two years of ongoing treatment are likely to be highly motivated to want to maintain their level of tolerance and therefore very likely to continue to include peanut in the diet. However, there may be concerns around the psychological stress and anxiety of consuming a food that has been diligently avoided for many years and previously greatly feared as a cause of potentially fatal reactions. Children and young people may need additional psychological support during the transition. High parental anxiety around the same issues is likely.
17. **Key issue 3:** Patient health state utility values **Questions:** Do you think assessment of health-related quality of life could differ depending on whether patients	Parents/carers of children may answer the questions with more consideration of their child's health-related quality of life. Adolescents may be answering with less emotional and intellectual maturity and could possibly be more dismissive of the impact their allergy has on their quality of life.

themselves (adolescents) or carers (children) complete it? If yes, in what way? Do you think assessment of health-related quality of life by parents or carers of children with peanut allergy could be capturing the impact of peanut allergy on their own quality of life, rather than on the quality of life of their children?	We feel the views of the parents reporting for their children should be considered and included. The parents/carers know their children best and should be able to report on the quality of life of their own children. If these reports are discounted, then the number of reports from adolescents is low and there would be no representation of the 4- to 11-year-old children at all.
18. **Key issue 4:** Resource use associated with anaphylactic reactions and adverse events. **Questions:** Would you expect the management (and therefore associated resource use) of severe anaphylactic reactions requiring adrenaline to differ depending on whether it was caused by accidental peanut exposure, or by treatment with Palforzia? Do you think that the severe but rare treatment-related adverse events may have impact on health-related quality of life and/or costs, and therefore should be included in the economic model?	We would not expect that the treatment for severe anaphylactic reactions would be any different for accidental exposure to Palforzia treatment. In practice, patients often report that emergency treatment for anaphylaxis falls far short of the best practice outlined in NICE CG134. All patients admitted to emergency care for treatment of anaphylaxis should receive the same standard of care regardless of the cause. However, patients receiving Palforzia are extremely well trained to recognise the signs of anaphylaxis and have their adrenaline auto-injectors on hand to use at the first indication of an allergic reaction which may well reduce the severity of the reaction. Treatment related adverse events may well have an effect on QOL/costs e.g. travel to hospital, lost parental work hours etc so should be included in costings.

19. Additional questions: How is peanut allergy currently being diagnosed? Would you expect any additional testing would be needed to assess suitability for treatment with Palforzia?	Children are usually referred to allergy specialist services where they are diagnosed with their peanut allergy. Where children have been seen in allergy services for some time, clinicians are best placed to assess the suitability of treatment. Clinicians will also be familiar with the family and their level of commitment to the treatment plan.
20. Are there any important issues that have been missed in ERG report?	N/A

PART 3 -Key messages

20. In up to 5 sentences, please summarise the key messages of your statement:

- This is a much needed and long-awaited technology
- Living with peanut allergy has a major impact on all aspects of daily life
- Treatment will alleviate the significant financial burden of living with severe peanut allergy
- Treatment is expected to significantly reduce the psychological burden of living with severe peanut allergy
- Potential reduction in allergic reactions will reduce NHS burden of treatment including emergency care

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Palforzia for treating peanut allergy [ID1282]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **20 September 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Anaphylaxis Campaign**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Timing of food challenges including the timing at which utility gains are realised in clinical practice	no	The suggestion of offering only one food challenge at 2 years post treatment initiation may be very difficult for patients to maintain motivation without any testing to evaluate effectiveness. Food challenge at 1 year post treatment initiation may be more realistic. Older teenagers will be moving through milestones such as starting secondary school, university etc and will likely want to know their allergy status to help them manage their allergy risk in new environments. Anaphylaxis Campaign feels that QOL benefits of improved peanut tolerance CAN be realised prior to food challenge – increasing tolerance could reduce severity of reactions to accidental exposures whether the patient is aware of their current tolerance level or not and awareness of this possibility may provide some relief from health related stress and anxiety.
Key issue 2: Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance.	**no**	The proportion of people and their carer's more likely to accept stopping treatment and transitioning to peanuts in the diet after 2 years (and a food challenge) is likely to be higher for those who reached treatment doses of 2000mg as opposed to those at the lower doses of 300mg, 600mg and 1000mg.

		Those young people aged 17 years and over would potentially be more likely to have peanuts in their diet to avoid “being different to their friends”, they are bigger risk takers and are more likely to be away from parental controls regarding diet. In addition, young people who have committed to two years of ongoing treatment are likely to be highly motivated to want to maintain their level of tolerance and therefore very likely to continue to include peanut in the diet. However, there may be concerns around the psychological stress and anxiety of consuming a food that has been diligently avoided for many years and previously greatly feared as a cause of potentially fatal reactions. Children and young people may need additional psychological support during the transition. High parental anxiety around the same issues is likely.
Key issue 3: Patient health state utility values	**no**	Parents/carers of children may answer the questions with more consideration of their child's health-related quality of life. Adolescents may be answering with less emotional and intellectual maturity and could possibly be more dismissive of the impact their allergy has on their quality of life. We feel the views of the parents reporting for their children should be considered and included. The parents/carers know their children best and should be able to report on the quality of life of their own children. If these reports are discounted, then the number of reports from adolescents is low and there would be no representation of the 4- to 11-year-old children at all.
Key issue 4: Resource use associated with anaphylactic reactions and adverse events	**no**	We would not expect that the treatment for severe anaphylactic reactions would be any different for accidental exposure to Palforzia treatment. In practice, patients often report that emergency treatment for anaphylaxis

		falls far short of the best practice outlined in NICE CG134. All patients admitted to emergency care for treatment of anaphylaxis should receive the same standard of care regardless of the cause. However, patients receiving Palforzia are extremely well trained to recognise the signs of anaphylaxis and have their adrenaline auto-injectors on hand to use at the first indication of an allergic reaction which may well reduce the severity of the reaction. Treatment related adverse events may well have an effect on QOL/costs e.g. travel to hospital, lost parental work hours etc so should be included in costings.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:		YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

Palforzia for treating peanut allergy [ID1282]

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We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **20 September 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

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- Do not include medical information about yourself or another person that could identify you or the other person.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Allergy and Clinical Immunology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Timing of food challenges including the timing at which utility gains are realised in clinical practice	YES	**The BSACI strongly recommends that a food challenge is undertaken prior to treatment initiation. The reasons for this include:** - **Many patients have a diagnosis made on the basis of allergy testing (which can be unreliable) rather than clinical history. Furthermore, up to 20% of peanut-allergic patients will outgrow their allergy in childhood, thus a food challenge prior to treatment is required to prevent unnecessary use of resources etc.** - **Around 40% of peanut-allergic individuals need a level of exposure ≥ ½ peanut to induce objective symptoms [Houben et al, Food Chem Toxicol. 2020 Dec;146:111831. doi: 10.1016/j.fct.2020.111831]. Therefore, there is a strong case for food challenge prior to treatment to identify those patients with higher reaction thresholds who do not need the technology.** - **Food challenges have great educational value and thus reduce the risks associated with future exposure, whether uncontrolled (ie. accidental reactions) or intentional (e.g. during oral immunotherapy) [see Burrell et al, Arch. Dis. Child. 2021;106:558-563].** **We therefore recommend that a food challenge is always undertaken prior to treatment. Whether a second food challenge is needed after initial treatment is arguable: a patient who can tolerate 300mg of peanut protein on a daily basis (ie. maintenance dose) is almost certainly going to be able to tolerate**

		300mg (equivalent to about 1½ peanuts) at food challenge. However, a food challenge would be needed to demonstrate tolerance beyond that amount, or to evaluate whether the treatment has resulted in longer-term sustained unresponsiveness (i.e. ongoing reduction in reactivity to peanut without daily maintenance dosing).
Key issue 2: Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance.	**YES**	**Our members have a variety of views as to duration of treatment required with the technology prior to converting to natural peanut-containing food products for regular dosing:** - **One (minority) perspective is that the technology should be used for all doses until point of discontinuation, on the basis that the amount of allergen in natural food products can vary (indeed, the weight of a peanut can vary by +/- 20%). However, the degree to which this natural variation is of clinical significance (compared to other factors which impact on efficacy and safety of oral immunotherapy, such as intercurrent infections, exercise) is unclear.** - **At the opposite extreme are clinicians who consider that it is inappropriate to charge significant amounts of money for a food product that essentially anyone can buy in a shop for a few pounds. Thus, the majority of our members felt that the technology should only be used for initial dosing (where doses administered cannot be reliably given using "natural food products", until patients can be transitioned to "real" foods e.g. peanuts, peanut-containing confectionery. There were 2 types of opinion expressed: either to transition to natural food once a patient can tolerate ½ peanut (about 100mg), or transition once an individual has reached the 300mg maintenance dose.** **At the same time, some patients/families are more reassured about the standardised dosing of the technology, as opposed to the variation in dose which might occur with transitioning to "real" foods. However, some members had extensive experience in transitioning to "real" foods in a**

		challenge scenario, which provided the necessary reassurance to patients and families. **Most recent data indicates that the majority of patients undergoing oral immunotherapy for peanut allergy require regular and ongoing doses to maintain treatment effect. Taste aversion of peanut is also a major factor, impacting on compliance. Studies are underway assessing the required frequency of dosing needed after initial treatment induction to maintain treatment effect: to our knowledge, there are currently no relevant data published with respect to the technology. Given existing expertise with immunotherapy for aeroallergens and clinical trials of peanut immunotherapy which have been published, it is very likely that at least 3 years treatment is required, although at least one group has demonstrated that a reduction in the frequency of doses after the first year of treatment can be undertaken without adversely impacting on clinical efficacy (Turner et al, abstract submitted to American Academy of Allergy, Asthma and Immunology Annual Meeting, AAAAI 2022).**
Key issue 3: Patient health state utility values	**YES**	**Quality of life is very likely to improve in part due to the experience of an allergic reaction under controlled circumstances [see Burrell et al, Arch. Dis. Child. 2021;106:558-563]. The same report also highlights significant discordance in the improvement in HRQL reported by peanut-allergic young people, compared to their parents. This supports the need to evaluate HRQL in both peanut-allergic individuals rather than just their parents. Around 1/3 of the improvement in quality of life with oral immunotherapy can be directed attributed to a food challenge undertaken prior to treatment initiation [Patel et al, J. Allergy Clin Immunol. 2020; doi.org/10.1016/j.jaci.2019.12.435]**
Key issue 4: Resource use associated with anaphylactic reactions and adverse events	**YES**	**BSACI agrees with the ERG that "all patients who require adrenaline due to an anaphylactic reaction would incur the same resource use (i.e., they would**

		need an ambulance and transport to hospital), regardless of whether the event was caused by treatment or by accidental exposure." **BSACI would be very concerned over any insinuation that:** **1) someone having anaphylaxis should not self-administer or be administered the first line treatment for anaphylaxis (i.e. IM adrenaline);** **2) that someone having anaphylaxis due to the technology and has been appropriately treated with IM adrenaline should then be managed in a different way from someone who has had anaphylaxis due to accidental peanut consumption.** **It should be noted, however, that there is interest in whether such a dogmatic approach will be needed in the future. First, the impact of COVID-19 has resulted in consideration of transport to hospital not being mandatory where an individual experiencing non-severe anaphylaxis responds quickly to a single dose of IM adrenaline e.g. see Casale et al, J Allergy Clin Immunol Pract. 2020 Jun;8(6):1795-1797. doi: 10.1016/j.jaip.2020.04.022. Likewise, in some clinical trials settings, patients with mild anaphylaxis reactions at home to treatment which respond rapidly to IM adrenaline may not require hospital attendance where video-conferencing is available: however, such decisions are made by a senior trials clinician and thus a similar process might not be feasible outside the clinical trials setting. In any event, there is currently no consensus on this amongst BSACI members.** **Any impression that anaphylaxis does not need treatment with adrenaline, and an adrenaline-treated reaction doesn't need an Emergency Medical Response is likely to be very controversial and unacceptable to the vast majority of healthcare professionals at the current time.**

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:		**NO**	**Costs of hospital visits in Table 62 seems to only include staff costs – but there are multiple additional costs involved which are not included** **Many of the costing used are over 5 years out of date, and with the requirement for social distancing, are likely to have increased.**

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Palforzia for treating peanut allergy [ID1282]

Critique of the Company's Response to Technical Engagement

Produced by Aberdeen HTA Group

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Date completed: **04 October 2021**

Contains: ■

Version: **1.0**

This report provides the ERG's critique of additional clarification and new evidence provided by the company, Aimmune Therapeutics, in response to the Technical Engagement phase of the appraisal and in advance of the first AC meeting for the topic. The company have accepted all but one of the amendments incorporated in the ERG preferred base case analysis. The one exception is issue 3, where the company prefers the use of pooled EQ-5D responses to generate health state utility values (pooled across carer proxy and adolescent self-report), whereas the ERG retains its preference for the use of adolescent self-report only. The commentary provided below addresses the key issues in turn and should be read in conjunction with the company and other stakeholder's submitted technical engagement responses, the ERG report, and the company submission.

Issue 1: Timing of food challenges including the timing at which utility gains are realised, and Palforzia treatment acquisition costs are incurred, in clinical practice.

The company and ERG preferred base cases are now aligned in applying the following assumptions in the economic model:

A) Utility benefits of Palforzia treatment can only be realised in clinical practice after the results of a food challenge (and hence knowledge of the maximum tolerated dose (MTD) of peanut) are known. Both the ERG and company base cases assume a single food challenge would occur, approximately 2 years after initiation of Palforzia treatment.
B) For patients treated by avoidance only, food challenges in clinical practice are unlikely, and thus the utilities associated with "current health" elicited from the company's utility study (assumed MTD<300mg) are applied to all patients in the avoidance arm.
C) The utilities associated with up-dosing and maintenance would not be realised in the avoidance arm of the model.
D) Palforzia treatment would continue up until the point that the results of a food challenge are known. Treatment would only be discontinued prior to this time point due to adverse reactions, and not due to improved tolerance levels.

Issue 2: Long term assumptions about treatment discontinuation, and transition from peanuts in diet to avoidance.

As noted in the ERG report, two areas of substantial uncertainty, and key drivers of the ICER are assumptions about A) the proportion of patients who discontinue Palforzia treatment after [redacted] years, moving to inclusion of peanuts in diet, thus accruing treatment benefit, but no treatment acquisition costs over time and B) the proportion of patients who subsequently revert from peanuts in diet to avoidance. Both model parameters were informed by clinical expert opinion, elicited using the SHELF framework.

For treatment discontinuation, the ERG questioned why additional weighting was given to the opinions of one clinical expert, as opposed to using the mean of all [redacted] participating clinical expert's initial stated parameter values. The company clarify that an iterative approach was used to achieve consensus, based on discussion and debate among the group after individual values were elicited. The company confirm that consensus was achieved by the whole group, around the values initially provided by one clinical expert. Given the further clarification from the company, the ERG is satisfied that the approach taken is reasonable.

The ERG also questioned the validity and derivation of the weighting of responsibility ([redacted]carers /[redacted]patients) for ensuring adherence to peanut in diet (i.e., the proportion who, having moved to peanut in diet, subsequently revert to avoidance only). The company clarify that the weighting was obtained from the clinical experts participating in the SHELF exercise. Full details are provided in the company response to technical engagement and the ERG is satisfied that the approach taken by the company is reasonable.

On balance, the ERG and company preferred base case parameters for the proportion discontinuing Palforzia treatment and the proportion subsequently reverting to peanut in diet are aligned. Whilst the ERG considers the company's methodology to be reasonable, there remains insufficient evidence, either from real-world observable data, or from the Palforzia clinical trials to robustly determine the true parameter values for the proportion and timing of Palforzia treatment discontinuation (transition to peanut in diet) and the proportion subsequently reverting to avoidance only. The impact of this uncertainty on the ICER is substantial, as illustrated in both the company and ERG conducted scenario analyses.

One additional uncertainty that arose during the response to technical engagement phase was around how clinicians would use Palforzia in clinical practice. The response received from the British Society for Allergy and Clinical Immunology indicates that the way in which palforzia might be used in clinical practice could vary widely and may be less extensive than the way in which treatment was used in the clinical trials and economic model. The majority view among the group's experts

was that Palforzia should only be used for the initial up-dosing phase, after which point patients could transition to peanuts in diet. The response stated that this transition may take place once patients demonstrate an MTD of 100mg or 300mg whilst receiving Palforzia. Stopping Palforzia at a MTD of 300mg, would reflect ceasing treatment at the end of the up-dosing phase of the economic model. Such a treatment scenario would allow earlier Palforzia treatment discontinuation, earlier transition to peanuts in diet by removing the maintenance phase of the model and would thus lead to substantially reduced Palforzia treatment acquisition costs. However, it is unclear what the most appropriate corresponding assumptions about treatment effectiveness should be. Whilst it is reasonable to assume that treatment effectiveness may be lower than that observed in the trials, the most appropriate magnitude of reduction for use in the economic model in this scenario is unclear.

Issue 3: Patient health state utility values

The company base case analysis obtains health state utility values by pooling data from all respondents to the utility survey (N=[redacted]), including adolescent (N=[redacted], N=[redacted] treatment naïve and N=[redacted] treatment experienced) self-report and carer proxy (N=[redacted]) reports of EQ-5D-Y health status. EQ-5D data were obtained for current health (assumed MTD<300mg), up-dosing, maintenance, and tolerance of 6-8 peanuts health states. The ERG considers the use of N=[redacted] adolescent self-reports to be more appropriate for decision making because EQ-5D is self-reported directly by patients with experience of peanut allergy. The ERG is concerned that using carer proxy reporting may mis-represent the true impact on patient QoL and may be at risk of double counting carer's anxiety associated with caring for someone with peanut allergy. Carer disutility is also incorporated in the model by directly eliciting carer responses to the EQ-5D for their own health status as part of the company's utility study. The company make several arguments in favour of the inclusion of carer proxy reporting (as outlined in the company's response to technical engagement):

Company argument 1: Using carer proxy responses is aligned with the NICE reference case when it is not possible to elicit patient values directly. The ERG agrees with the general premise of this statement. However, the ERG view is that EQ-5D-Y responses elicited directly from adolescents with experience of peanut

allergy more closely aligns with the NICE reference case than carer proxy responses.[1]

Company argument 2: The company notes that where data are available from both adolescents (self-reporting) and carers providing proxy values, that the health state utility values derived from the EQ-5D-Y responses are broadly similar. The ERG accepts that this is correct, in the case where data are available from both adolescents and carer proxy reports. However, it is unclear whether this observation could be extrapolated to a sample of carers providing proxy values, who do not have adolescents also taking part in the study. Indeed, given the differences in the ERG and company preferred base case analyses, it is reasonable to assume that carers proxy values do differ, depending on whether adolescents from the same family are also providing responses in the study.

Company argument 3: The company note that, within the PALISADE clinical trial, responses to the FAQLQ disease specific HRQoL measure were similar for both patient self-report and carer proxy reports. The company suggest that this provides evidence that the ERG's concerns about double counting may be unfounded. However, the ERG remains unconvinced as to whether these findings can be extrapolated to EQ-5D-Y response reporting.

Company argument 4: The company view is that differences in the ERG and company preferred utilities is more likely due to the method of response elicitation than who provided the responses. The company note that respondents taking part in structured interviews (n=[redacted]) yielded higher utility gains between MTD<300mg and tolerance of 6-8 peanuts states than respondents taking part in the online survey (n=[redacted]). The company view is that the interviews may provide more robust data, where concepts could be explained in greater detail by the facilitators. The ERG's understanding is that all the adolescent's responding to the study done so via the online survey. Whilst the ERG accepts that, in general, in-person interviews may provide more robust data than online surveys, they are not without their limitations (for example social desirability or acquiescence bias). On balance, the ERG considers the benefits of obtaining data directly from adolescents with experience of

peanut allergy to outweigh any limitations of using online surveys as opposed to structured online interviews.

Company argument 5: The company consider the responses pooled across adolescent self-report and carer proxy report to be more inline with the utilities used in the "sensitized" and "desensitized" states of the ICER-US model for peanut allergy (including Palforzia)[2]. However, the ERG notes that the health state descriptions do not directly align with the current model, the details of the measurement exercise are not directly compared by the company, the ICER-US model did not use the UK valuation set to derive utilities and the source study used in the ICER-US report relates to all food allergies, not just peanut[2,3]. Therefore, the ERG does not consider this comparison to be a sufficient ground on which to support the use of carer proxy values in the current assessment.

Company argument 6: The company suggest that the results from carer proxies are more aligned with other research suggesting that the DALY burden from peanut allergy is greater than from uncomplicated type 1 diabetes[2]. The ERG does not consider this argument to be robust as it is a somewhat selective, narrow assessment of the evidence, and it would quite likely be feasible to make counterarguments, using alternative data or diseases that would support the use of different values.

Overall, the ERG notes the company's arguments, but on balance, does not consider the arguments to be sufficiently robust to warrant a change in the ERG preferred base case source of utility data. That is because acceptance of any of these arguments would necessitate accepting the use of carer proxy data, when directly reported EQ-5D-Y responses are available from an adolescent sample with experience of peanut allergy. The ERG believes therefore that the data used in the ERG preferred base case analysis are more consistent with the NICE reference case[1].

If the committee were to prefer direct adolescent self-reports only, the company argue that the full sample of adolescent self-reports (including N=[redacted] treatment naïve and N=[redacted] palforzia treatment experienced respondents) should be considered. The

ERG disagrees with the company's suggestion for two reasons. Firstly, the data for the treatment naïve and treatment experienced respondents were obtained using different methodology. For the N=[redacted] treatment experienced sub-sample, the health state utility value for the MTD: <300mg, up-dosing and maintenance health states were obtained by asking respondents to retrospectively recall what their EQ-5D responses would have been pre-trial, during up-dosing and during maintenance respectively. The ERG is concerned that the methodology used is subject to a substantial risk of recall bias. Whilst the duration of recall is unclear, the utility study suggests that it may be several years. The ERG therefore does not consider these data to be appropriate for decision making. Secondly, HSUVs based on treatment naïve, and treatment experienced respondents are substantially different, as detailed in Table 1 below. The ERG queries the face validity of the values obtained from the treatment experienced sample, especially for the MTD: <300mg health state.

Table 1 Alternative utility values considered for use in the economic model

	Company base case, Adolescent and carer proxy pooled (N=[redacted]) EQ-5D Mean (SE)	**ERG base case, Adolescent, treatment naïve, (N=[redacted]) EQ-5D Mean (SE)**	**Adolescent, treatment experienced (N=[redacted]) EQ-5D Mean (SE)**	**Company scenario post TE, Adolescent, pooled (N=[redacted]) EQ-5D Mean (SE)**	**ERG scenario post TE [A]**
Current HRQoL (MTD: <300mg state)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts (MTD: 2000mg and peanuts in diet states)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG: Evidence review group; HRQoL: Health related quality of life; MTD: Maximum tolerated dose; SE: standard error; TE: Technical engagement.

[A] ERG scenario analysis uses the sample for N=[redacted] respondents for current HRQoL, up-dosing and maintenance (where recall biases for N=[redacted] treatment experienced respondents are greatest). The analysis pools treatment naïve and treatment experienced for the tolerance state of 6-8 peanuts for the committee's information.

Whilst the ERG does not consider the pooled treatment naïve and treatment experienced responses to be appropriate for valuing the MTD:<300mg, up-dosing and maintenance states, it could be argued that pooling data for the tolerance of 6-8 peanuts may be reasonable, given that the EQ-5D reporting for the treatment experienced sub-sample for this state is based on "current health" and is therefore not likely to be subject to the same recall biases described above. The ERG therefore conducts a scenario analysis applying treatment naïve adolescent self-report for the MTD: <300mg, up-dosing and maintenance states, but pooling all adolescent self-report data together for the tolerance 6-8 peanuts state. The results of the additional scenario analyses applied to the ERG base case are reported in Table 2 below.

Table 2 Additional ERG conducted scenario analyses

Analysis	**Incremental costs**	**Incremental QALYs**	**ICER**
Company original base case ICER	19,769	0.916	21,581
Company revised base case ICER (following technical engagement)	20,458	0.862	23,745
ERG preferred deterministic ICER (company revised base case + HSUVs based on adolescent self-report.	20,458	0.559	36,565
ERG utility scenario analysis (See Table 1 above)	20,458	0.596	34,343

Abbreviations: ERG: Evidence review group; HSUV: Health state utility values; ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life years

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Palforzia for treating peanut allergy [ID1282]

ERG Critique of the Company's Response to Technical Engagement

[ADDENDUM]

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Date completed: **29 October 2021**
Version **2.0**
Contains: [redacted]

Overview:

This addendum updates the ERG's critique of the company's (Aimmune Therapeutics) response to Technical Engagement phase of the appraisal. The addendum details the ERG's further critique and scenario analyses requested by the appraisal lead team and NICE at the pre-meeting briefing (PMB) for this topic.

Company revised base case following technical engagement:

As noted in the ERG critique of technical engagement, the company updated their base case analysis to reflect all of the ERG's preferred assumptions, apart from the preferred source of utilities. The company provided an updated deterministic ICER but did not provide a probabilistic analysis alongside their updated base case. The ERG re-run the probabilistic analyses and provide deterministic and probabilistic analyses for both the company's updated base case and ERG preferred base case analyses in Table 1 below. Figures 1 and 2 provide the scatter plot and cost-effectiveness acceptability curves (CEACs) for the company's updated base case analysis.

Table 1: Company and ERG preferred ICERs

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ / QALY gained)**
Company revised base case following technical engagement (Deterministic)					
Avoidance	11,874	19.117	**-**	**-**	**-**
Palforzia + Avoidance	32,332	19.979	20,458	0.862	23,745
Company revised base case following technical engagement (Probabilistic)					
Avoidance	11,815	19.106	-	-	-
Palforzia + Avoidance	34,618	19.985	22,803	0.879	25,940
ERG preferred base case (Deterministic)					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	32,332	20.338	20,458	0.559	36,565
ERG preferred base case (Probabilistic)					
Avoidance	11,799	19.774	-	-	-
Palforzia + Avoidance	34,537	20.347	22,738	0.573	39,716

Abbreviations: ICER = Incremental cost-effectiveness ratio; QALY = Quality adjusted life years.

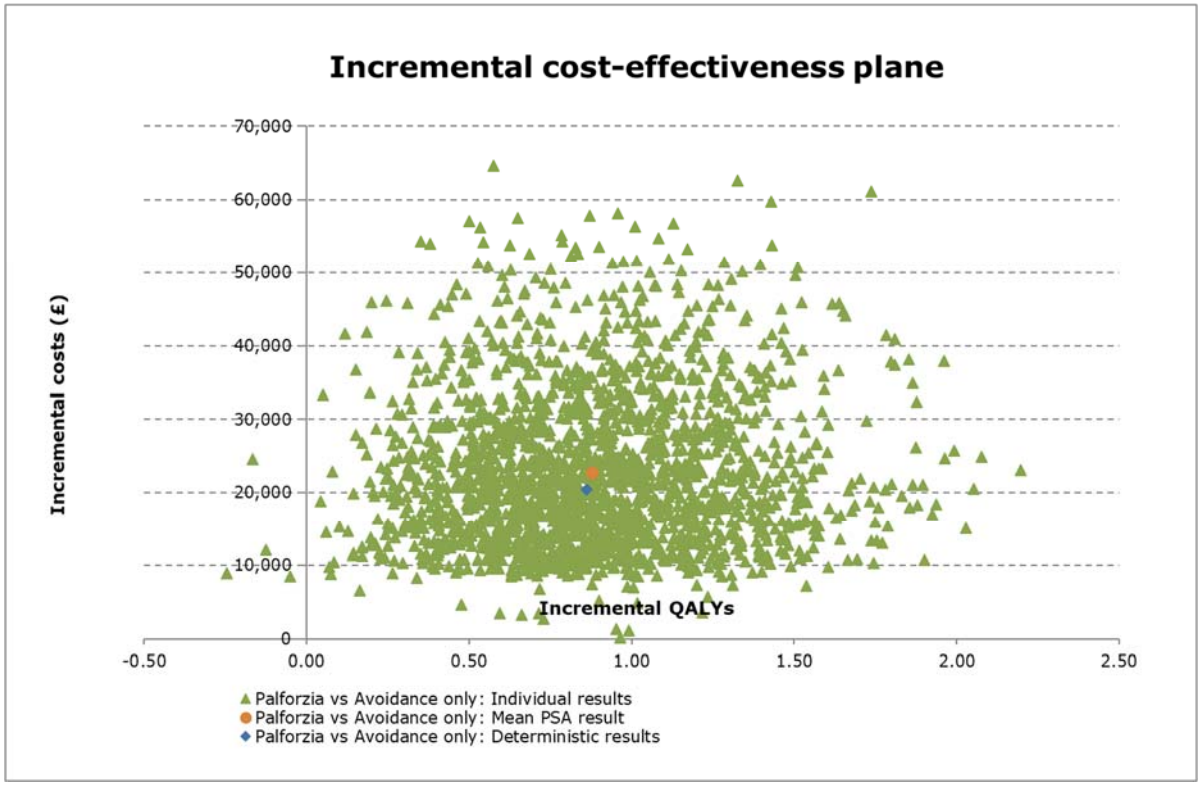

Figure 1: Company updated base case: Incremental cost-effectiveness plane (re-produced from company economic model post technical engagement)

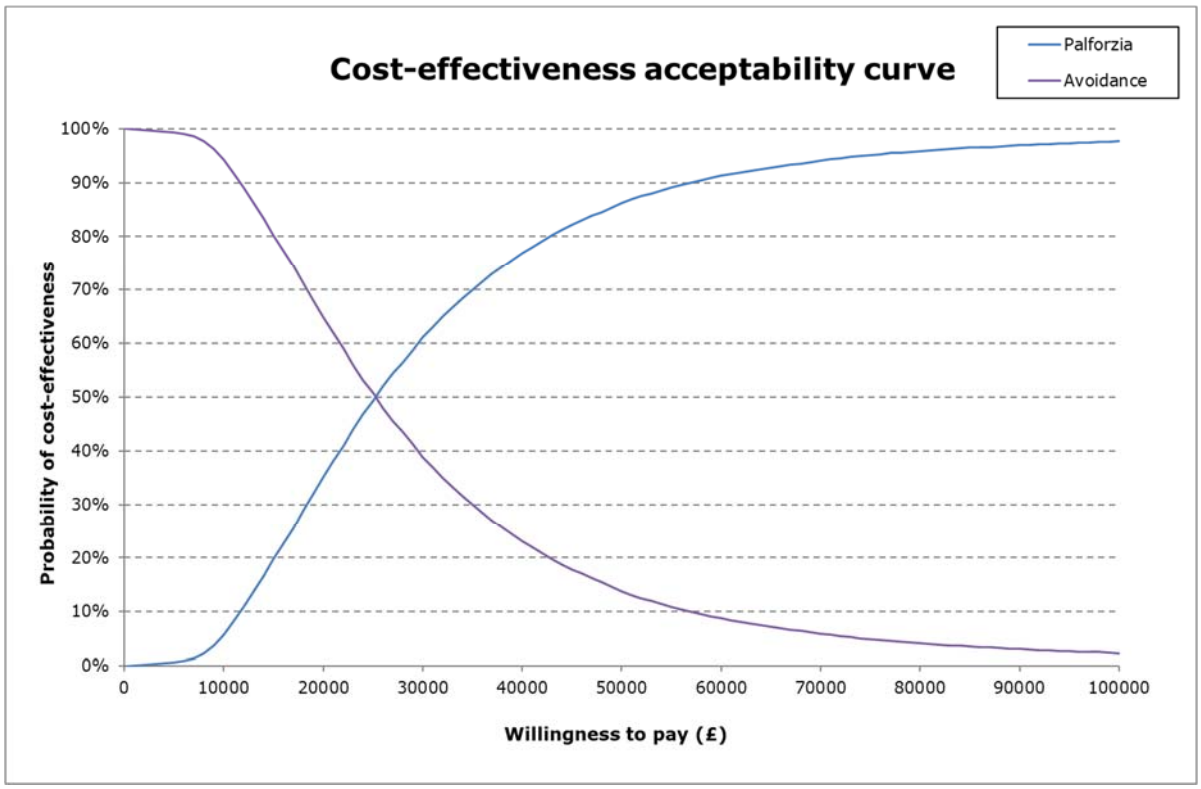

Figure 2: Company updated base case: Cost-effectiveness acceptability curve (re-produced from company economic model post technical engagement)

ERG additional scenario analyses for first appraisal committee meeting

Spontaneous tolerance:

After entry into the extrapolation phase of the model (i.e., from cycle 31 onwards), the model assumes that the cohort maintain their tolerated dose of peanut unless they discontinue treatment (either entering the avoidance state or transitioning to regular inclusion of peanuts in diet) or achieve a 'spontaneous tolerance'. The company base case model assumes that 5% of patients will grow out of their allergy over their lifetime, applied continuously in each model cycle. The 5% estimate was suggested by the company and was confirmed as appropriate by the clinical experts partaking in the SHELF elicitation exercise. The experts agreed that most resolutions occur among the youngest children and that 5% in the target population was reasonable. The assumption is applied independently of treatment arm and health state.

The ERG notes that the BSACI guidelines quote a life-time spontaneous resolution of 21%, obtained from data across several studies[1,2,3]. One weakness of these studies was that the initial peanut allergy diagnosis was not based on food challenges, so it is difficult to determine if all participants definitively had peanut allergy. Another study found that of those with a confirmed peanut allergy (food challenge) at age 1, 22% had achieved spontaneous tolerance by age 4, the minimum age for which Palforzia is licensed[4]. Another study found that cumulative spontaneous tolerance occurs mostly in younger patients, with 22% achieving tolerance by age 8, and 27% achieving tolerance by age 12[5]. Of those who achieved a spontaneous tolerance, 80% did so by the age of 8. The ERG's clinical expert also confirms that most patients who outgrow their peanut allergy will do so in early childhood. The ERG notes that the current evidence base around lifelong spontaneous tolerance is sparse and of variable quality. However, the ERG is satisfied that the company's base case estimate of 5% lifelong tolerance among an average cohort starting age of 10 is reasonable, in line with expectations of clinicians in this population, and is consistent with the available published evidence.

The impact on the ICER of applying a 10% and 20% spontaneous tolerance rate is negligible because it is applied to all patients independently of treatment arm and

health state, and it is assumed that patients no longer incur the treatment costs of Palforzia once they enter the spontaneous tolerance state.

Food challenge

Clinical expert feedback at technical engagement suggested that clinicians may be reluctant to commence Palforzia treatment without first having confirmation of peanut allergy because some patients may 'grow out' of their allergy and hence a food challenge would be required to determine if treatment was still necessary. The ERG explores a scenario where the costs of an additional food challenge are applied in the first cycle of the Palforzia arm of the model. The impact is a small increase in the ICER.

Two year stopping rule

Clinical expert opinion received in response to technical engagement cast some doubt on the likelihood that patients would continue to receive Palforzia treatment over a full lifetime horizon. The ERG therefore explores the impact on the ICER of discontinuing Palforzia treatment in all patients after 2 years. The ERG notes that the timepoint for discontinuation may vary in clinical practice and notes that some clinical expert opinion obtained at technical engagement suggested that discontinuation may occur earlier (e.g., at the end of the up-dosing phase when a MTD of 300mg was achieved). However, the discontinuation timepoint of two years was chosen for this scenario analysis because it aligns with the follow up extension of PALISADE and with the ERG and company preferred timing of a food challenge to evaluate treatment progress.

The first scenario re-distributes the [redacted] that would have continued Palforzia between avoidance ([redacted]) and peanuts in diet ([redacted]) based on the proportions obtained from the SHELF clinical expert elicitation exercise. The assumption here is that the proportion reverting to avoidance is independent of whether a patient would have continued Palforzia or not.

The second scenario assumes, if a stopping rule was applied, that all those patients who would have continued Palforzia if it was available ([redacted]) would move to a strategy of avoidance. The ERG's justification for this scenario is that, based on the

company's expert elicitation exercise, the estimate of [redacted] of patients that remain on Palforzia treatment at [redacted] years reflects a subgroup of patients who would be reluctant or unwilling to include peanuts within their regular diet, and so might wish to continue Palforzia treatment instead of trying to include peanut in their diet. It may be more realistic to assume that if treatment was withdrawn from this patient sub group, that they would all revert to avoidance only.

Note that for both ERG scenario analyses, re-allocation from peanuts in diet to avoidance is assumed to occur over [redacted] years as per the company and ERG preferred base case analyses. The impact of both scenario analyses is a substantial reduction in the ICER, but the magnitude of that reduction is dependent on uncertain assumptions about whether this subgroup would move to avoidance or peanuts in diet.

Additional scenario analyses around patient health state utility values

The ERG has conducted several additional scenario analyses around the use of different subgroups of respondents completing EQ-5D in the company's utility study to generate health state utility values for use in the economic model. The company's preferred base case approach is to pool responses: a) across adolescent self-reported and carer proxy reported responses, b) across treatment naïve and palforzia experienced (AR101) subgroups and c) across structured interviews and an online survey. The ERG's preferred approach uses responses from treatment naïve adolescents on the grounds that carer proxies are inconsistent with the NICE reference case when alternative self-report data exist[6], and that the treatment experienced subgroup are subject to significant recall biases that cast doubt on the validity of the responses obtained.

The ERG conducts a further three scenario analyses to explore these uncertainties further:

1. Using a pooled sample of adolescent self-report and carer proxy report, but excluding N=[redacted] participants from the AR101 study, whose reported EQ-5D responses were likely subject to substantial recall bias,

2. Responses from interview participants only and

3. Responses from online survey participants only

The different HSUVs obtained from these participant groups are reported alongside the company and ERG preferred base case analyses in Table 2 for comparison. Table 3 shows a comparison of the corresponding carer utilities with a) base case, b) treatment naïve only, with removal of AR101 study utilities subject to recall bias, c) for the interview sample only and d) for the online survey sample only.

The impact on the ICER of all additional scenario analyses undertaken is provided in Table 4.

Table 2: Alternative patient health state utility values for use in the economic model

	Company base case Adolescent + carer Interview + survey Treatment naïve + AR101 Mean (SE); N=[redacted]	**Adolescent + carer, Interview + survey AR101 Mean (SE); N=[redacted][A]**	**Alternative scenario Adolescent + carer, Interview + survey Treatment naïve Mean (SE); N=[redacted]**	**Alternative scenario Adolescent + carer, Interview only Treatment naïve Mean (SE); N =[redacted]**	**Alternative scenario Adolescent + carer Survey only[C] Treatment naïve Mean (SE); N=[redacted]**	**ERG base case Adolescent only Survey only Treatment naïve, Mean (SE); N=[redacted]**
Current HRQoL (MTD: <300mg state)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts (MTD: 2000mg + pid states)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[A] included for information, not included as an additional scenario analysis.

Table 3: Alternative carer utility values for use in the economic model

	Company & ERG base case Interview + survey Treatment naïve + AR101 Mean (SE)	Alternative scenario Interview + survey Treatment naïve Mean (SE)	Alternative scenario Interview only Treatment naïve Mean (SE)	Alternative scenario Survey only Treatment naïve Mean (SE)
Current HRQoL (MTD: <300mg state)	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts (MTD: 2000mg + pid states)	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Impact of scenario analyses around spontaneous tolerance rate

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ / QALY gained)
ERG preferred base case					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	32,332	20.338	20,458	0.559	36,565
Scenario analysis 1: 10% spontaneous tolerance					
Avoidance	11,741	19.787	-	-	-
Palforzia + Avoidance	32,047	20.342	20,306	0.555	36,607
Scenario analysis 2: 20% spontaneous tolerance					
Avoidance	11,482	19.805	-	-	-
Palforzia + Avoidance	31,494	20.350	20,012	0.545	36,693
Scenario analysis 3: Include the costs of an additional food challenge at baseline prior to commencing Palforzia treatment					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	32,608	20.338	20,734	0.559	37,059
Scenario analysis 4: Apply a two-year stopping rule and re-distribute those stopping to peanuts in diet: Long-term health state occupancy among survivors: Palforzia (0%), peanuts in diet [redacted], avoidance [redacted] [A]					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	20,714	20.312	8,840	0.534	16,555

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ / QALY gained)
Scenario analysis 5: Apply a two-year stopping rule and re-distribute all those stopping Palforzia to avoidance: Long-term health state occupancy among survivors: Palforzia (0%), peanuts in diet [redacted], avoidance [redacted] [A]					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	20,542	20.223	8,668	0.445	19,494
Scenario analysis 6: HSUVs pooled adolescent and carer proxy respondents, pooled interview and survey, treatment naïve only (N=[redacted]					
Avoidance	11,874	19.298	-	-	-
Palforzia + Avoidance	32,332	20.036	20,458	0.738	27,735
Scenario analysis 7: HSUVs pooled adolescent and carer proxy respondents, interview only, treatment naïve only (N=[redacted]					
Avoidance	11,874	19.424	-	-	-
Palforzia + Avoidance	32,332	20.292	20,458	0.868	23,562
Scenario analysis 8: HSUVs pooled adolescent and carer proxy respondents, survey only, treatment naïve only (N=[redacted]					
Avoidance	11,874	19.258	-	-	-
Palforzia + Avoidance	32,332	19.923	20,458	0.665	30,756
Scenario analysis 9: Carer disutilities, treatment naïve only					
Avoidance	11,874	19.778	-	-	-
Palforzia + Avoidance	32,332	20.342	20,458	0.563	36,307

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ / QALY gained)
Scenario analysis 10: Carer disutilities, interview sample only					
Avoidance	11,874	19.578	-	-	-
Palforzia + Avoidance	32,332	20.170	20,458	0.592	34,554
Scenario analysis 11: Carer disutilities, online survey sample only					
Avoidance	11,874	19.879	-	-	-
Palforzia + Avoidance	32,332	20.426	20,458	0.547	37,382
Carer disutility, assume one carer only					
Avoidance	11,874	19.947	-	-	-
Palforzia + Avoidance	32,332	20.448	20,458	0.502	40,789
Remove all carer disutility					
Avoidance	11,874	20.142	-	-	-
Palforzia + Avoidance	32,332	20.577	20,458	0.434	47,119

Abbreviations: ICER = Incremental cost-effectiveness ratio; QALY = Quality adjusted life years.

[A] Base case analysis, long-term extrapolation health state occupancy for comparison: palforzia: (█%), peanuts in diet (█%), avoidance (█%)

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