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.

Table of contents

List of Tables

List of Figures

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.

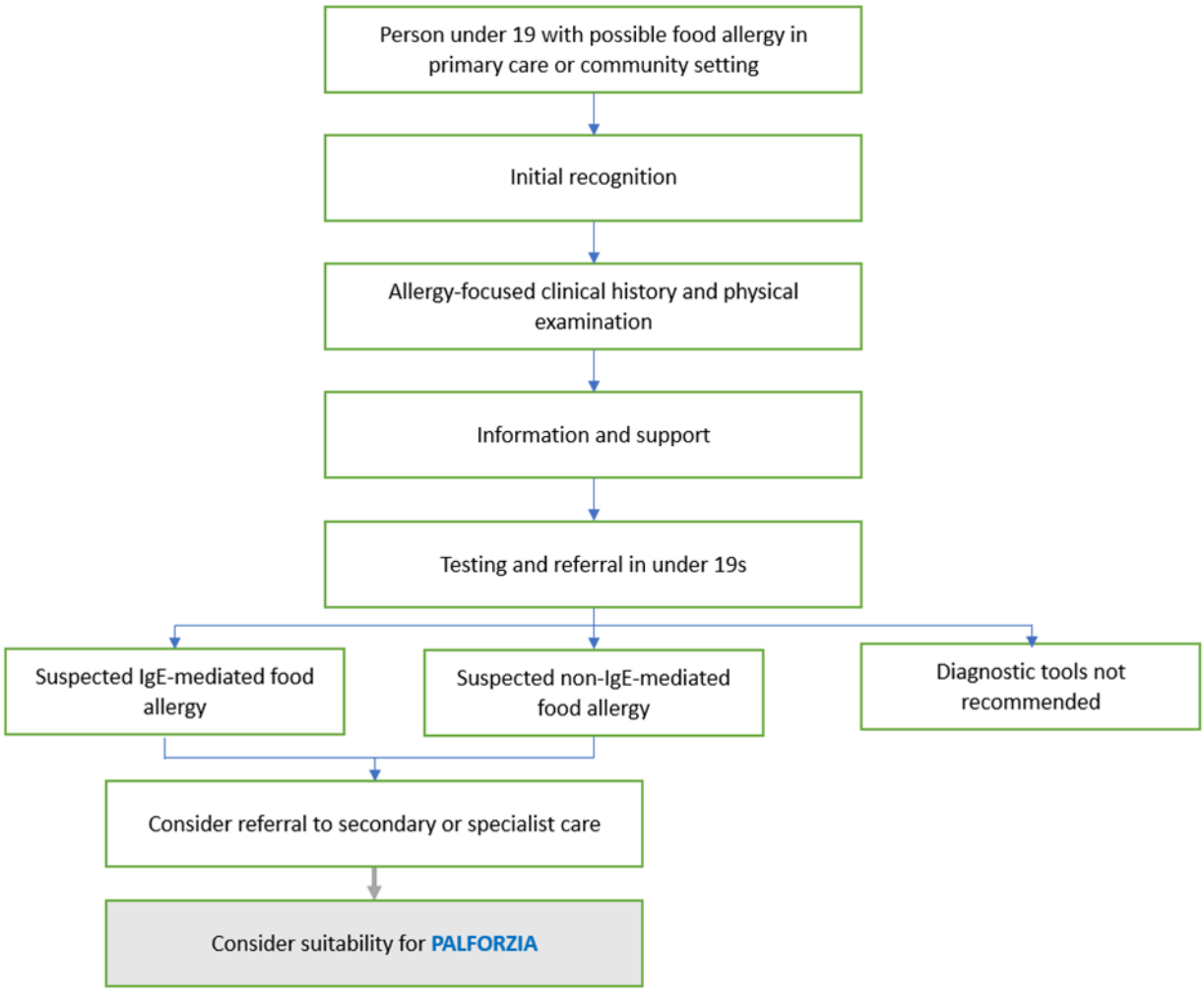


Figure 1 Proposed pathway of care of peanut allergy with Palforzia (within the NICE pathway)

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

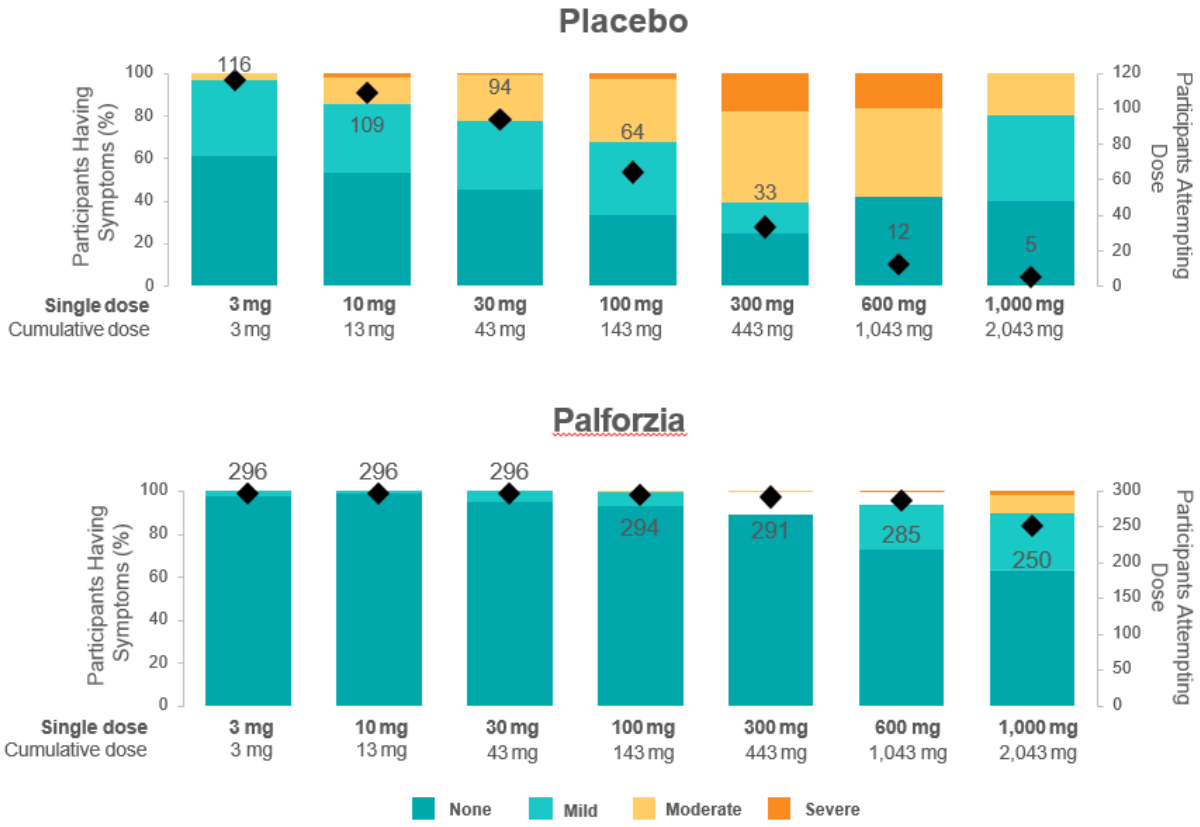
	PALISADE		ARC004		ARTEMIS		*ARC001	
	Palforzia (n=372)	**Placebo (n=124)**	**Cohort 1 (n=103)[a]**	**Cohort 3A (n=26)[a]**	**Palforzia (n=132)**	**Placebo (n=43)**	**Palforzia (n=29)**	**Placebo (n=26)**
Tolerance of 1000mg, % (95%CI)	50.3 (45.2, 55.3)	2.4 (0.8, 6.9)	80.6 (71.6, 87.7)	96.2 (80.4, 99.9)	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

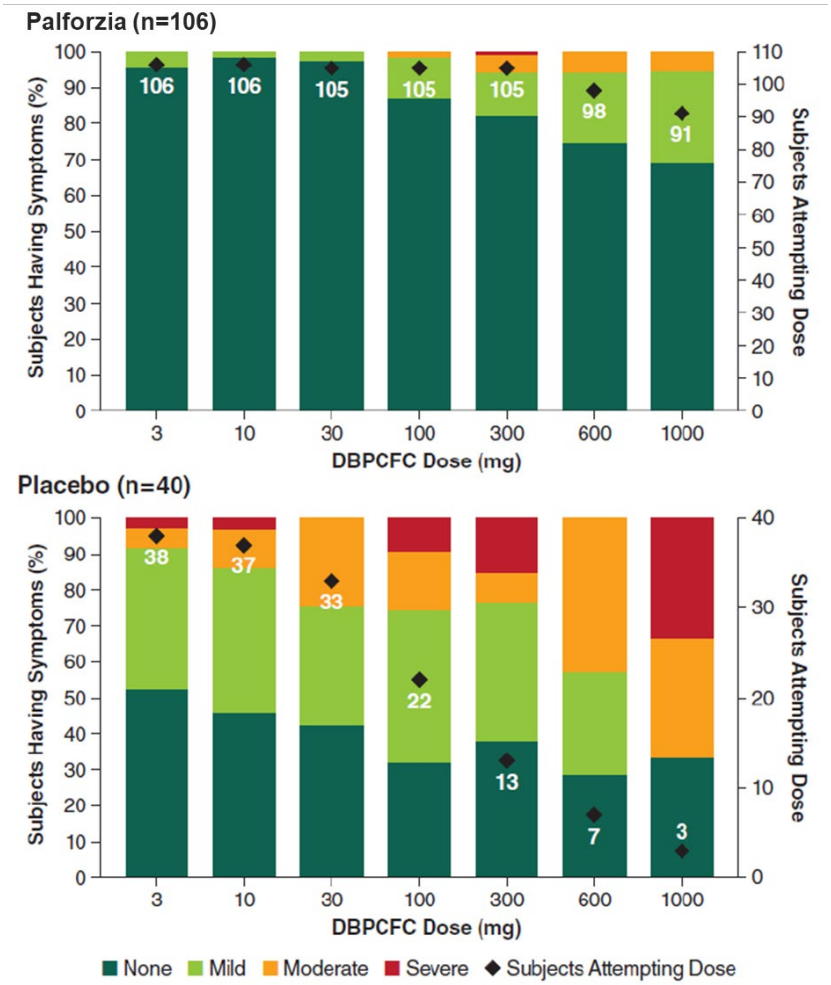
Other efficacy endpoints reported in the CS are as follows:

- **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]

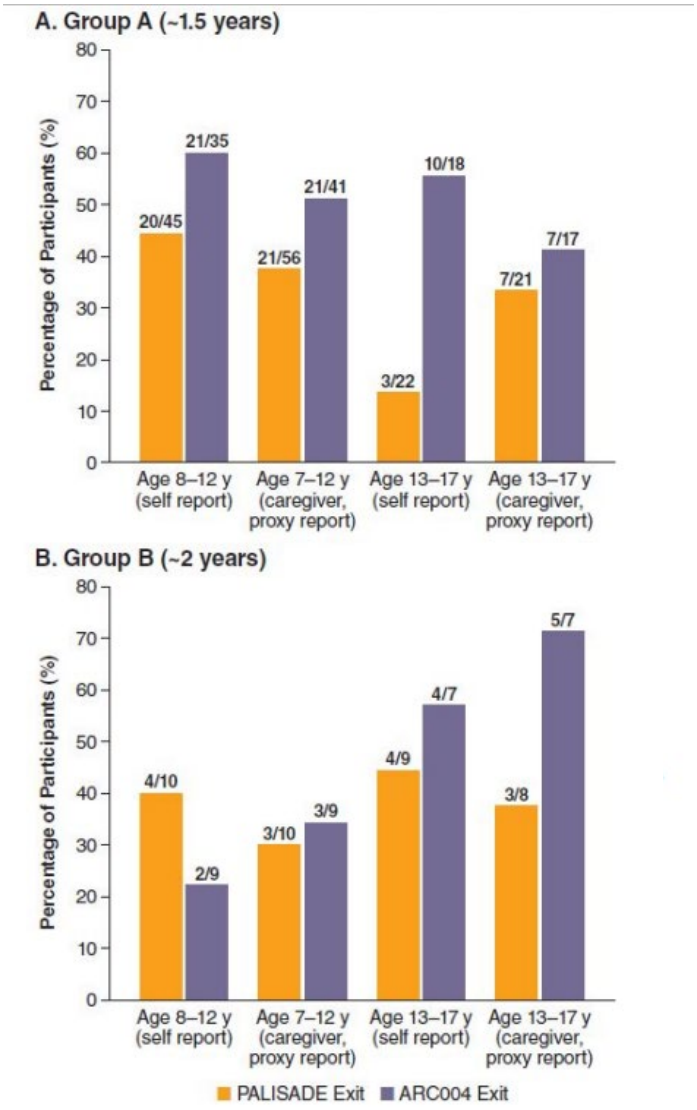
Rates of accidental food allergen exposure were higher in ARC004 than in PALISADE or ARTEMIS: [redacted] in Cohort 1 and [redacted] in Cohort 3A. The CS reported that the rates of accidental exposure to peanut requiring treatment were [redacted] in Cohort 1 and [redacted] in Cohort 3A and that [redacted] 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).

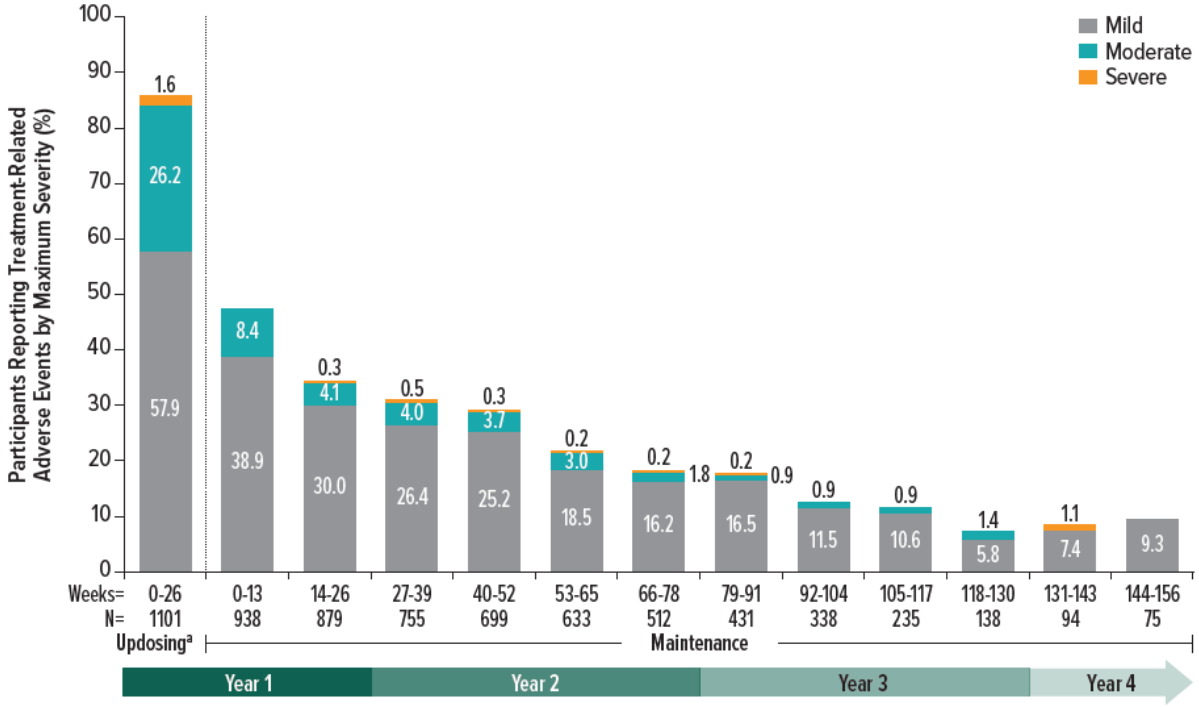
The pooled safety data indicate that the incidence of TEAEs was higher during up-dosing phase (85.7%) but both incidence and severity declined during maintenance treatment. Most adverse reactions to Palforzia were mild to moderate and in keeping with the safety profile of Palforzia and an oral

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.

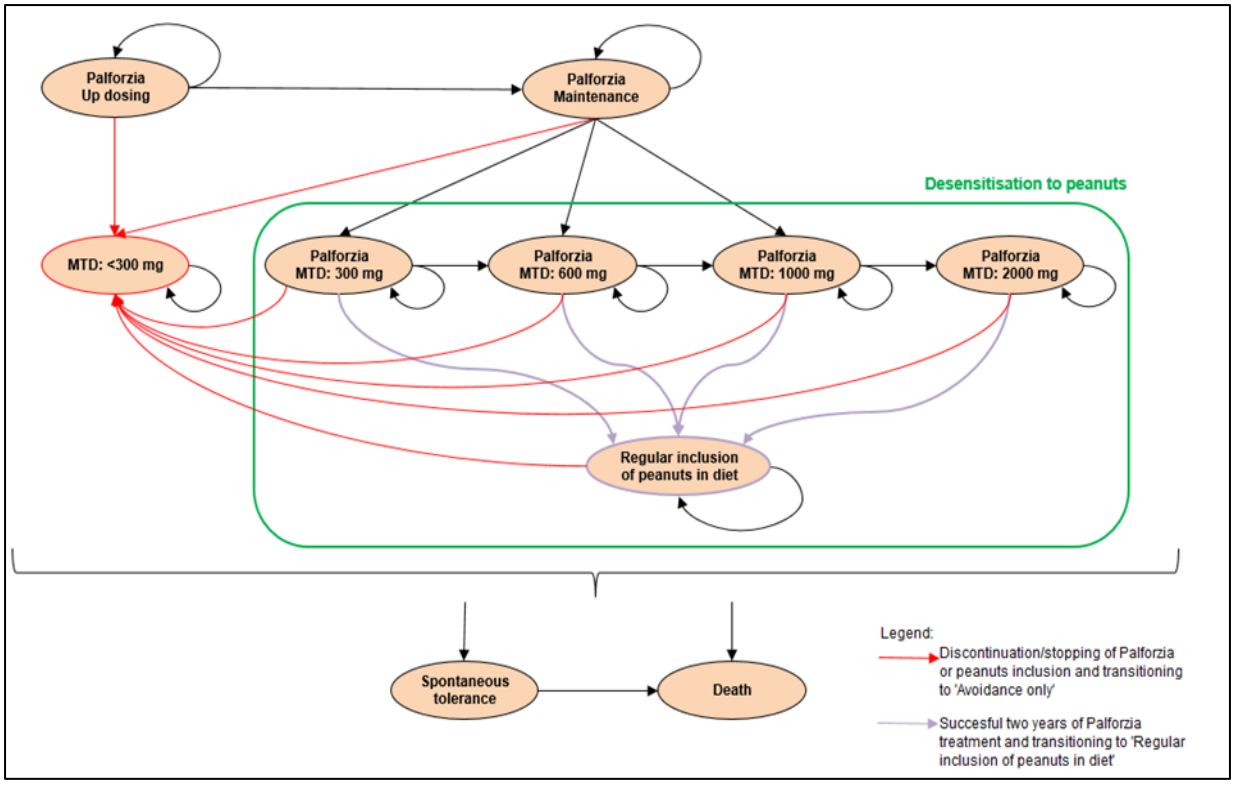


Figure 6. Palforzia arm model structure [reproduced from Figure 24, Document B of the CS)

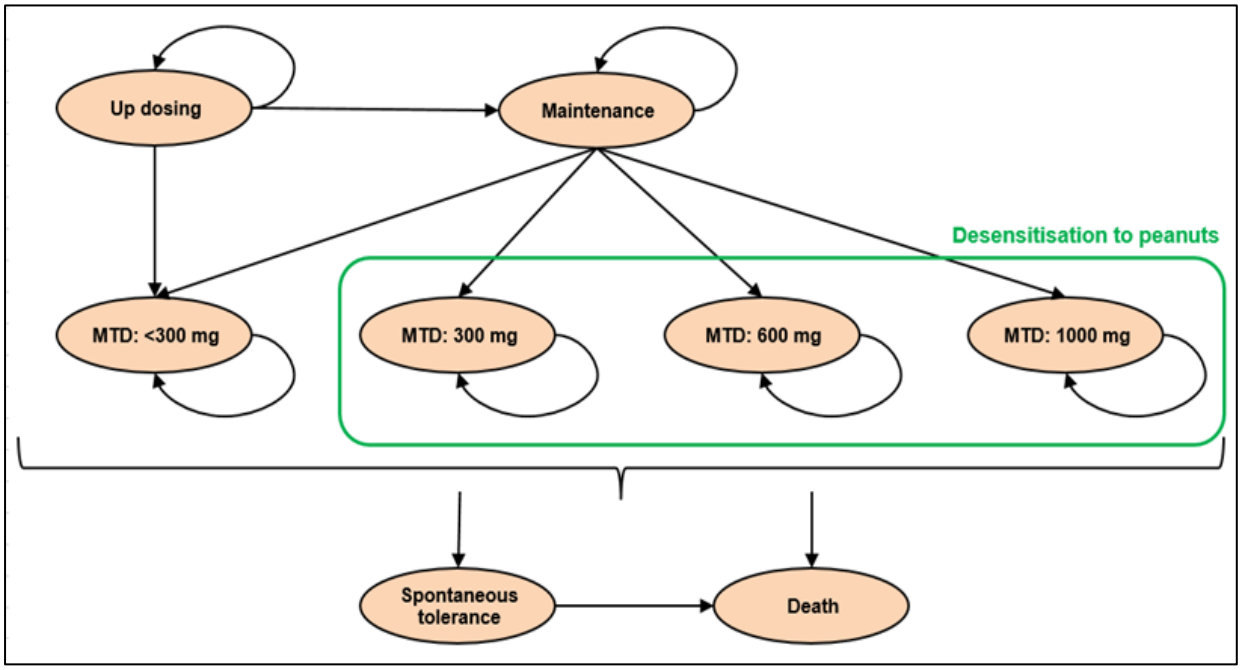


Figure 7. Avoidance arm model structure [reproduced from Figure 25, Document B of the CS)

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**

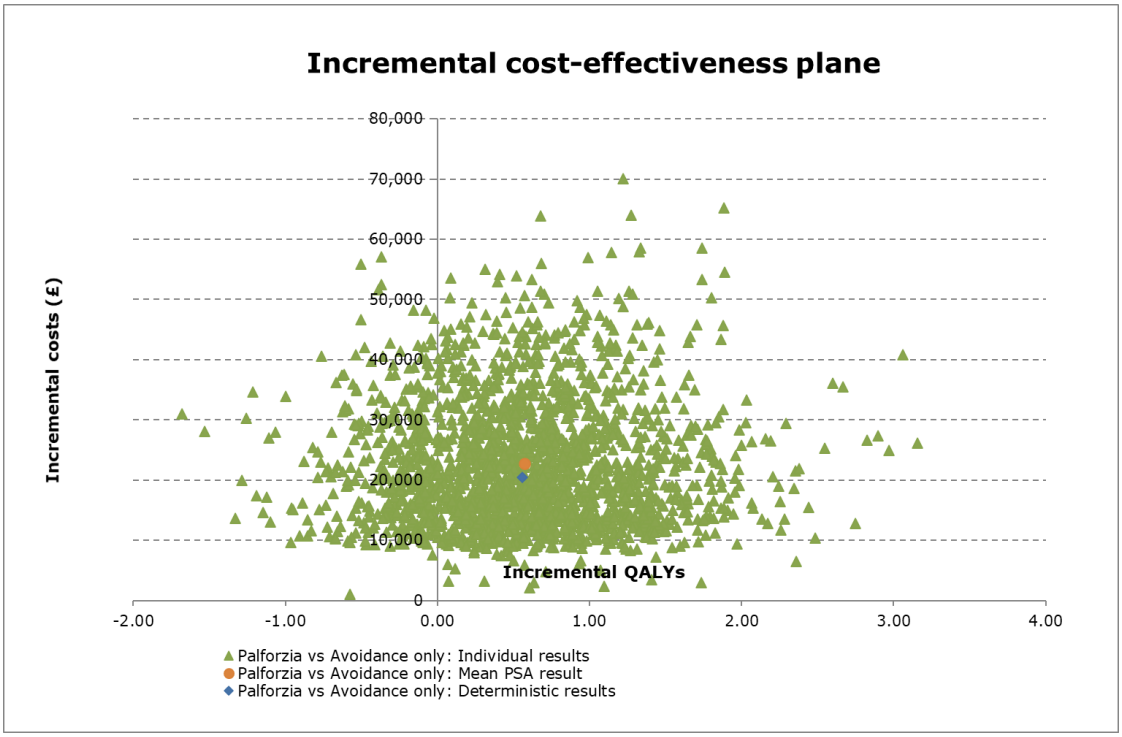


Figure 8 Scatter plot of cost-effectiveness plane using ERG preferred base case ICER [reproduced directly from the company submitted economic model]

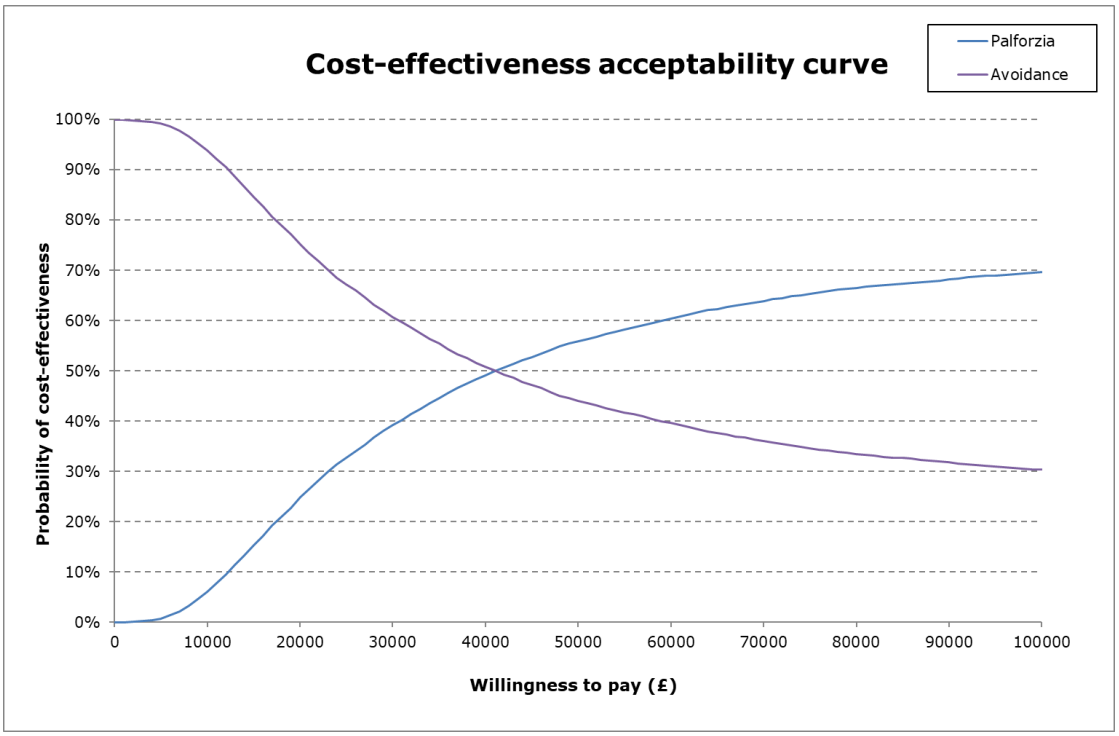


Figure 9 Cost-effectiveness acceptability curve using ERG preferred base case ICER [reproduced directly from the company's submitted economic model]

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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