For public – redacted

NICE National Institute for Health and Care Excellence

Palforzia for treating peanut allergy in children and young people

Lead team presentation

1st appraisal committee B meeting
Chair: Amanda Adler
Lead team: Nick Latimer, Veline L'Esperance, Tony Wootton
ERG: Aberdeen HTS Group
Technical team: Catherine Spanswick, Ewa Rupniewska, Nicole Elliott, Richard Diaz
Company: Aimmune Therapeutics UK Ltd
4 November 2021

Key issues

- How would NHS deliver treatment with Palforzia?
  - How many oral peanut challenge(s) to determine eligibility or response?
  - Duration of treatment with Palforzia?
- What is long-term natural history after Palforzia?
  - What percentage of people will include dietary peanuts after completing treatment?
  - What percentage will switch back to avoiding peanuts?
- All gains in quality adjusted life year relate to quality of life (utility). What is the most appropriate way to estimate values in young patients and their carers?

Background

Disease background – peanut allergy

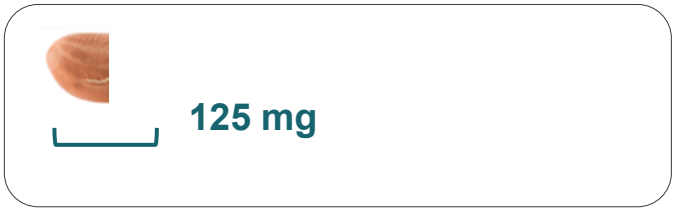
Can be life-threatening

- One of most common IgE-mediated food allergies
  - Affects 0.5% to 2% of children in UK
- Severe reactions can include anaphylaxis
  - Of fatal food-induced anaphylaxis, peanut allergy accounts for 16% of cases in children and 22% in adults
- Symptoms
  - angioedema - facial swelling
  - respiratory symptoms - including wheezing
  - conjunctivitis
  - oral allergy syndrome - lip/tongue swelling
  - rhinitis - blocked stuffed nose
  - urticaria - blotchy red rash
- Not possible to predict probability/severity of reaction based on previous reactions

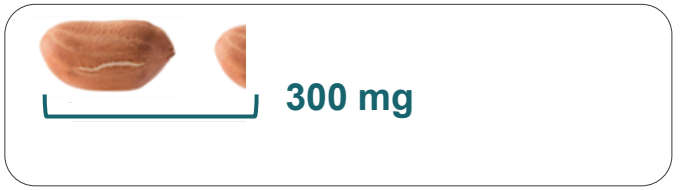
Tolerance to peanut protein may prevent or lessen reactions to accidental exposure to peanuts

Trials use food challenge with peanut protein as endpoints

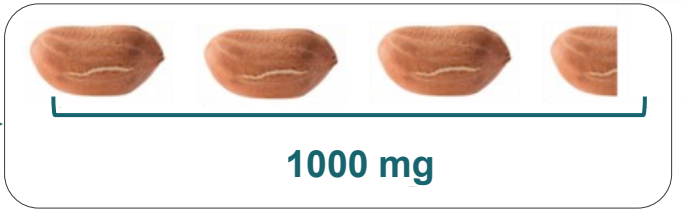
125 mg peanut protein ~½ peanut: median response-causing dose in epidemiological study[a]



300 mg: clinical expert – tolerating 300 mg = 'bite-protection' from small accidental exposures – meaningful outcome



1000 mg: tolerating 1000 mg protects ~8-fold; Clinical expert: highly clinically significant



- Trial endpoints: accidental exposure to peanut uncommon
  - one study: ~12% annual incidence in children with peanut allergy[b]

→ **oral food challenge** is surrogate endpoint, accepted by regulatory agencies

- **Oral food challenge** uses increasing doses of peanut protein to assess desensitisation. Tolerability threshold is highest dose with mild symptoms only

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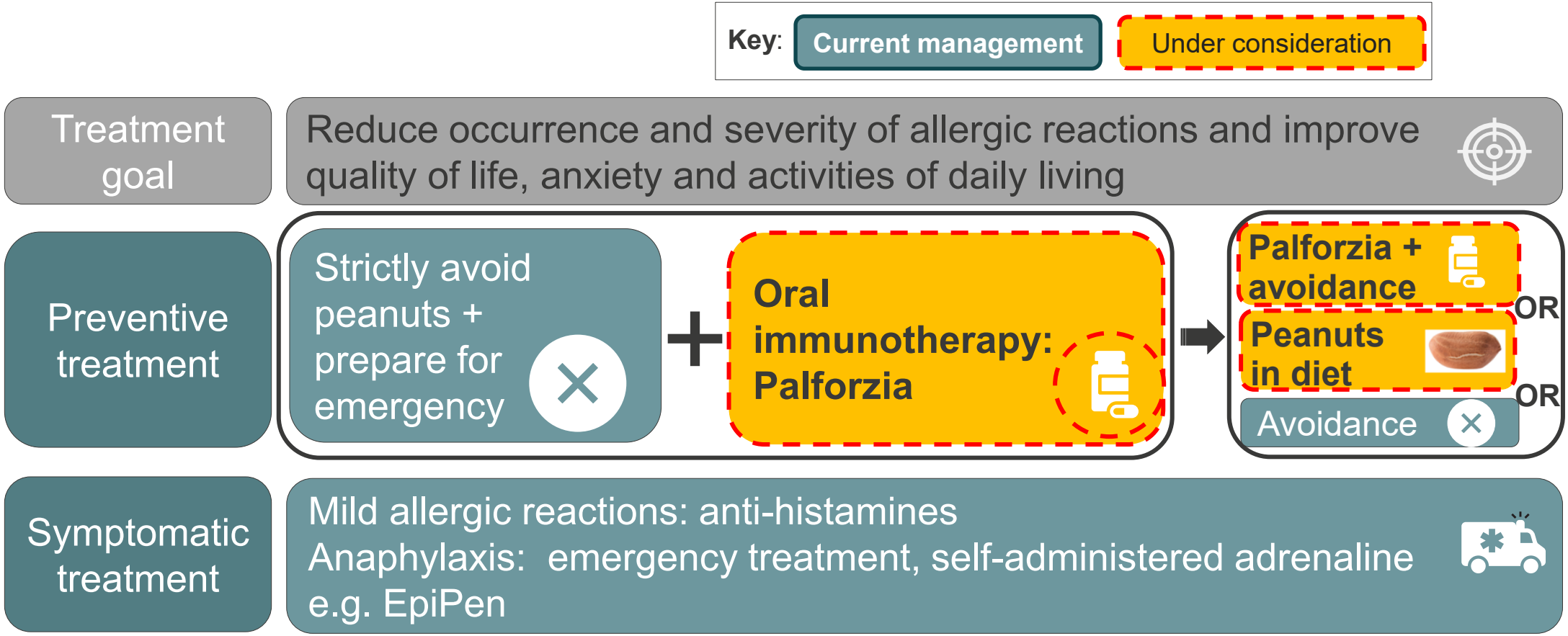
[a] Deschildre et al. (2016) Clin Exp Allergy 46(4):610-620; [b]Cherkaoui et al. (2015) Clin Translat Allergy 5:16.

Prevention and treatment pathway

No preventative treatment other than avoiding peanuts



NICE guidance – NICE Pathway (2020) Food allergy in under 19s; CG116 (2011) Food allergy in under 19s; CG134 (2020) Anaphylaxis: assessment and referral after emergency treatment.

◉ *Is the treatment pathway correctly represented?*
Is an alternative such as peanut flour used in clinical practice?
Should this be considered a comparator to Palforzia?

After Palforzia

Regularly taking Palforzia or including peanuts in diet needed to maintain tolerance

Clinical experts:

- Most patients on oral immunotherapy ‘desensitisation’ need ongoing doses to maintain treatment effect
- People who do not adhere to regularly including peanuts in diet may **lose tolerance**
- Not adhering to peanuts in diet linked to: aversion to taste, lack of motivation, adverse effects, restrictions around meals and exercise, lack of support
- Carers responsible for helping children to adhere, and may help adolescents to adhere

Patient expert:

- People will be motivated to include dietary peanuts after committing to Palforzia
- Psychological stress and anxiety about eating food diligently avoided and greatly feared for years. Psychological support may be needed after treatment– for children + carers

Clinical expert perspectives

- No **disease-modifying** treatments for peanut allergy at present – avoiding peanuts is not a treatment
- Most food allergy clinics structured as **diagnostic services**
- Palforzia – first oral immunotherapy treatment – **profound implications for allergy service delivery,** requiring investment
  - Care pathways
  - Infrastructure
  - Staffing
  - Operating costs
  - Capacity

Patient and carer perspectives

Comments from Allergy UK and Anaphylaxis Campaign

Impact of food allergy

- Affects ‘all aspects of daily life’ for individuals and families
- Impacts shopping and preparing food, weaning infants, eating out, travelling, seasonal events, education, work
- Teens and young people greater risk of dying from severe food allergic reactions than older people with food allergy
- ‘Can cause extreme anxiety’

People would like

- Treatment that addresses root cause of peanut allergy, not just acute allergic reaction
- To reduce ‘psychological burden of living with severe peanut allergy’

re: Palforzia

- ‘Much needed... long-awaited technology’
- Potentially life changing impact on individuals and families
- Could alleviate ‘financial burden of living with severe peanut allergy’
- Could reduce burden on emergency care

Palforzia (Aimmune Therapeutics UK Ltd)

Does not specify reintroducing peanuts into diet

Marketing authorisation	Age 4 to 17 years with confirmed peanut allergy; may continue > age 18. In conjunction with peanut-avoidance diet
Dosage and administration	Oral capsules up to 240 mg, or powder sachet 300 mg • **Start + dose escalation**: 5 dose levels in 1 day, 0.5 mg to 6 mg • **Up-dosing**: 11 dose levels, 2 weeks each, 3 mg to 300 mg • **Maintenance**: 300 mg once daily 1st ever dose and 1st dose of each new level given in clinic prepared to manage anaphylaxis
Duration	'Daily maintenance is required to maintain the tolerability and clinical effects of PALFORZIA.' 'Efficacy data currently are available for up to 24 months …' 'No recommendation can be made about duration of treatment beyond 24 months'
Mechanism	Oral immunotherapy. Palforzia is proprietary name for 'AR101', peanut protein defatted powder of *Arachis hypogaea L*.
Average list price per course of treatment	Flat price for each Palforzia dose range 0.5 to 300 mg: [redacted]. **No** patient access scheme (discount) to the NHS

NICE ◉ *When would treatment stop, if ever?*

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	Children with peanut allergy aged 4-17 years Adults who started treatment as children	Children aged 4 to 17 with a **confirmed diagnosis of peanut allergy who are under the care of a specialist physician**, includes those who turn 18 years old during therapy
Intervention	Palforzia	
Comparators	Clinical management without Palforzia including avoiding allergen, symptomatic treatments such as antihistamines and emergency medication	
Outcomes	• peanut allergy desensitisation • systemic allergic reactions including anaphylaxis • frequency and severity of symptoms after accidental exposure to peanuts • stopping treatment • adverse effects of treatment • health-related quality of life	As per the scope Note: • health-related quality of life considered for: - children - carers

- *Is company's proposed target population appropriate?*
- *How would peanut allergy desensitisation be measured in clinical practice?*

Clinical effectiveness

Clinical evidence

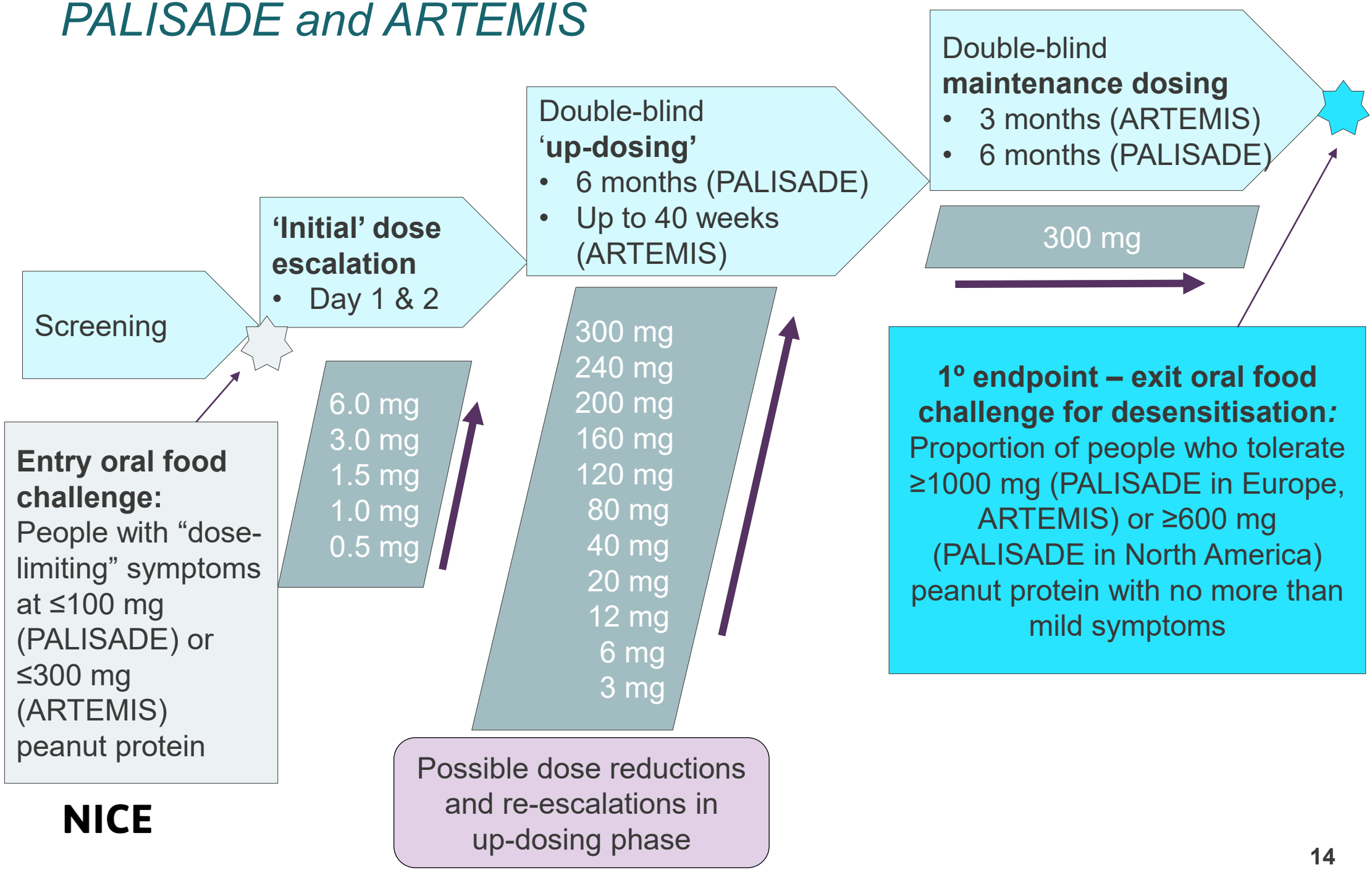
Populations differ in 2 trials; endpoint –food tolerance test peanut protein

	PALISADE (ARC003)	ARTEMIS (ARC010)	PALISADE follow-on (ARC004)
Trial / study	**Trials:** phase III, randomised, double-blind, placebo-controlled, multicentre		**Observational**: open-label follow-on to PALISADE
Population with peanut allergy	Age: 4 to 55 years • Sensitive to ≤100 mg peanut protein	Age: 4 to 17 years • Sensitive to ≤300 mg peanut protein	• Assigned to Palforzia + tolerated 300 mg dose at oral food challenge, **or** • Assigned to placebo + completed oral food challenge
Intervention	Palforzia		Palforzia
Comparator	Placebo		none
1º endpoint	% who tolerate ≥1000 mg (in PALISADE, Europe only)		Treatment-related adverse events
2º and other endpoints	• Tolerate ≥600 mg or ≥300 mg • Frequency and severity of symptoms after accidental exposure to peanut • Systemic allergic reactions • Treatment discontinuations • Adverse events		• Tolerate ≥2000 mg, ≥1000 mg, ≥600 mg or ≥300 mg • Frequency and severity of symptoms after accidental exposure • Systemic allergic reactions • Treatment discontinuations
Quality of life	Age-specific versions of Food Allergy-Related Quality of Life Questionnaire self-reported and parent-proxy reported and Food Allergy Independent Measure		

Company excluded Phase 2 ARC001 study from its modelling (small sample size and US-only study)

Palforzia trial design

PALISADE and ARTEMIS



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Trial participants – aged 4 to 17 years

Baseline characteristics

	PALISADE		ARTEMIS	
	Palforzia (N=372)	Placebo (N=124)	Palforzia (N=132)	Placebo (N=43)
Age, median [years]	9	9	[redacted]	[redacted]
4 to 11 years, n (%)	238 (64)	89 (72)	97 (74)	30 (70)
12 to 17 years, n (%)	134 (36)	35 (28)	35 (27)	13 (30)
Male, n (%)	208 (56)	76 (61)	68 (52)	27 (63)
Geographical region, n % North America Europe • UK	[redacted] NR	[redacted] NR	[redacted]	[redacted]
Peanut specific IgE, kUA/L [median (Q1, Q3)]	[redacted]	[redacted]	43.5 (5.2, 147.0)	69.7 (20.7, 103.0)
Prick test wheal diameter, mm [median (Q1, Q3)]	[redacted]	[redacted]	10 (8, 12)	10 (8, 13)
MTD peanut protein[a] ≤30 mg ≤100 mg	[redacted]	[redacted]	[redacted]	[redacted]

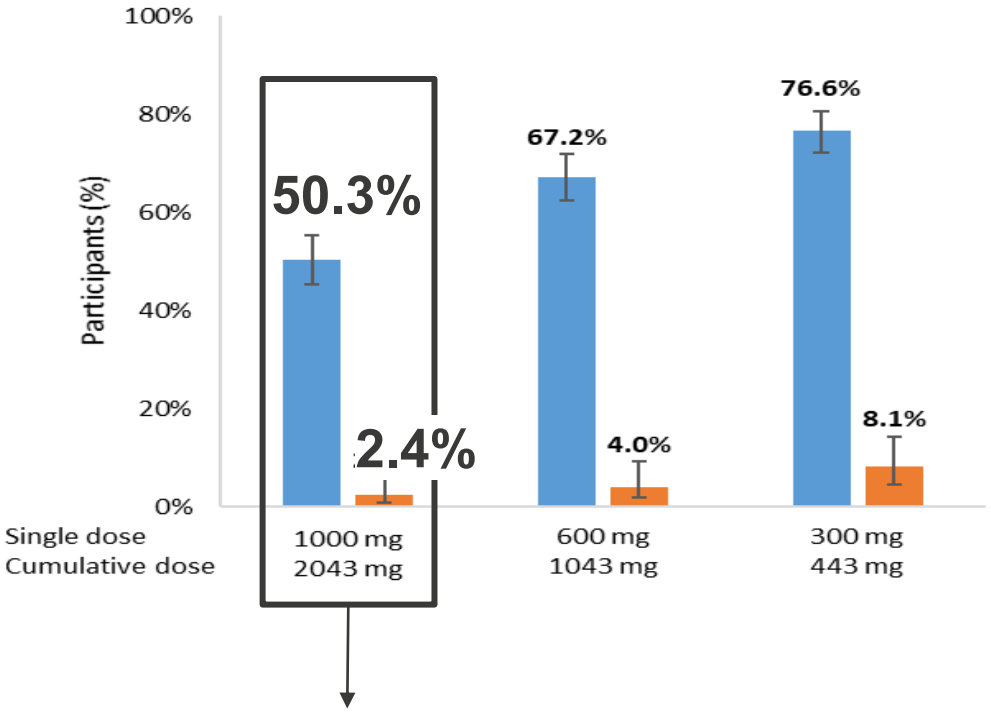
[a] Single highest tolerated dose of peanut protein at entry oral food challenge test.
IgE: immunoglobulin E, MTD: maximum tolerated dose, NR: not reported, Q: quartile.

◉ *Generalisable to NHS?*

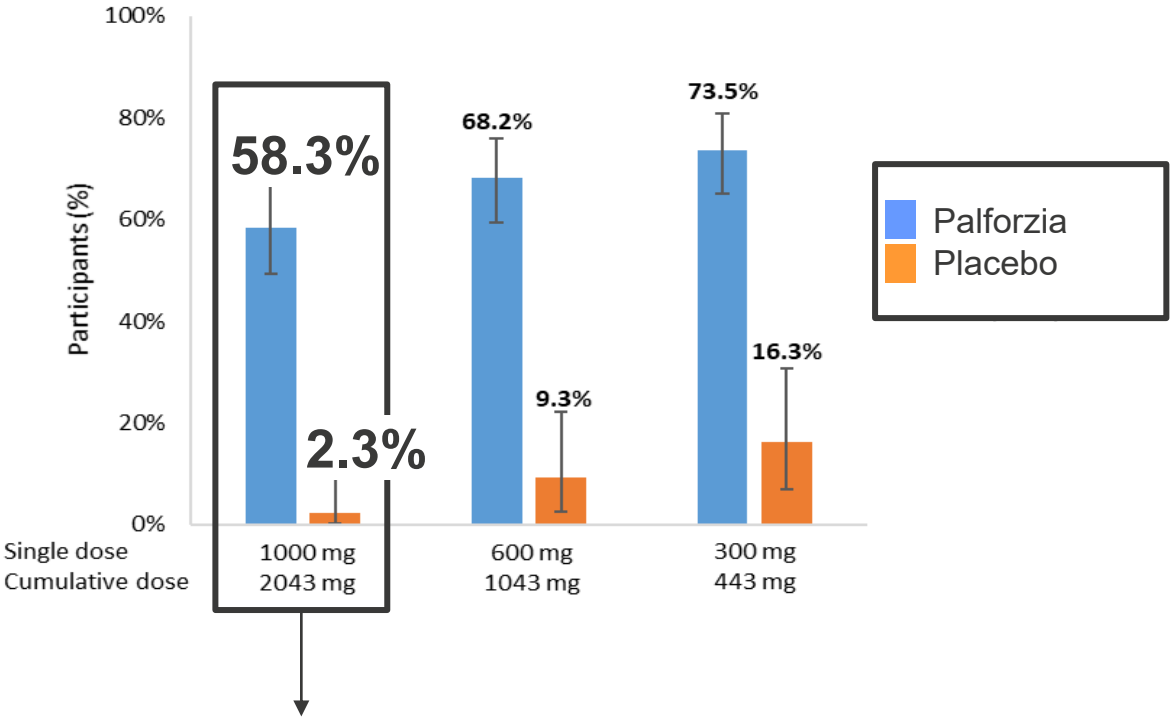
Results for people aged 4 to 17 years

Palforzia more effective than placebo: 1º efficacy endpoint met in both studies; supported by key 2º outcomes

PALISADE: % peanut desensitisation



ARTEMIS: % peanut desensitisation



1º endpoint in Europe
Absolute difference between treatments:
47.8% (95% CI: 38.0, 57.7; p<0.0001)

1º endpoint
Absolute difference between treatments
56.0% (95% CI: 44.1, 65.2; p<0.0001)

Clinical experts: tolerating 1000 mg peanut protein 'highly clinically significant'; tolerating 300 mg peanut protein 'meaningful outcome', gives 'bite protection'

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Neither company nor ERG meta-analysed trials

Model uses results from PALISADE, scenario with results from ARTEMIS

Company: meta-analysis not robust because of differences in designs

ERG: unable to confirm – no details provided; pooling data possible but no greater insight

Study design	PALISADE	ARTEMIS	ARC001[a]
Location	US, Canada, Europe	Europe	US
Age group	4 to 55 years (4 to 17 years used in economic modelling)	4 to 17 years	4 to 26 years
Inclusion criteria peanut protein: sensitivity test	≤100 mg	≤300 mg	≤143 mg
1º endpoint	Desensitisation – Europe: tolerate 1000 mg	Desensitisation: tolerate 1000 mg	Treatment-related adverse events
Duration maintenance treatment	6 months	3 months	None
	Informed company's base case cost-effectiveness modelling	Company used in scenario	Company did not use in modelling

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◉ *What is the best way to use all the data ?*

[a]Bird et al. (2018) JACI 6(2):476-485.

Accidental exposure to peanut

Low accidental exposure during maintenance; no evidence Palforzia prevents anaphylaxis

During maintenance, n (%)	PALISADE In ~6 months		ARTEMIS In ~3 months	
	Palforzia	Placebo	Palforzia	Placebo
Accidental exposure to peanuts	[redacted]	[redacted]	[redacted]	[redacted]
Reactions needing any treatment	[redacted]	[redacted]	[redacted]	[redacted]
Reactions needing treatment with adrenaline	[redacted]	[redacted]	[redacted]	[redacted]

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Note: total patient numbers for this analysis were not reported in company submission.
Abbreviations: N/A, not available (not provided)

Adverse events in people aged 4 to 17 years

Few serious treatment-emergent adverse events; no deaths

Palforzia: more adverse events affecting GI tract, respiratory tract, skin, and immune system, versus placebo group[a]

Participants with adverse event(s), n (%)	PALISADE		ARTEMIS	
	Palforzia (N=372)	Placebo (N=124)	Palforzia (N=132)	Placebo (N=43)
≥1 treatment-emergent adverse event	367 (99)	118 (95)	130 (99)	42 (98)
Mild	129 (35)	62 (50)	66 (50)	24 (56)
Moderate	222 (60)	55 (44)	63 (48)	18 (42)
Severe or higher	16 (4)	1 (1)	1 (1)	0
≥1 anaphylactic reaction				
Mild	23 (6)	1 (1)	8 (6)	1 (2)
Moderate	29 (8)	3 (2)	8 (6)	0
Severe (anaphylaxis)	1 (0)	2 (2)	0	0
Withdrawal due to treatment-emergent adverse events	43 (12)	3 (2)	14 (11)	1 (2)

◉ *Would adverse events require more frequent follow-up in clinic?*

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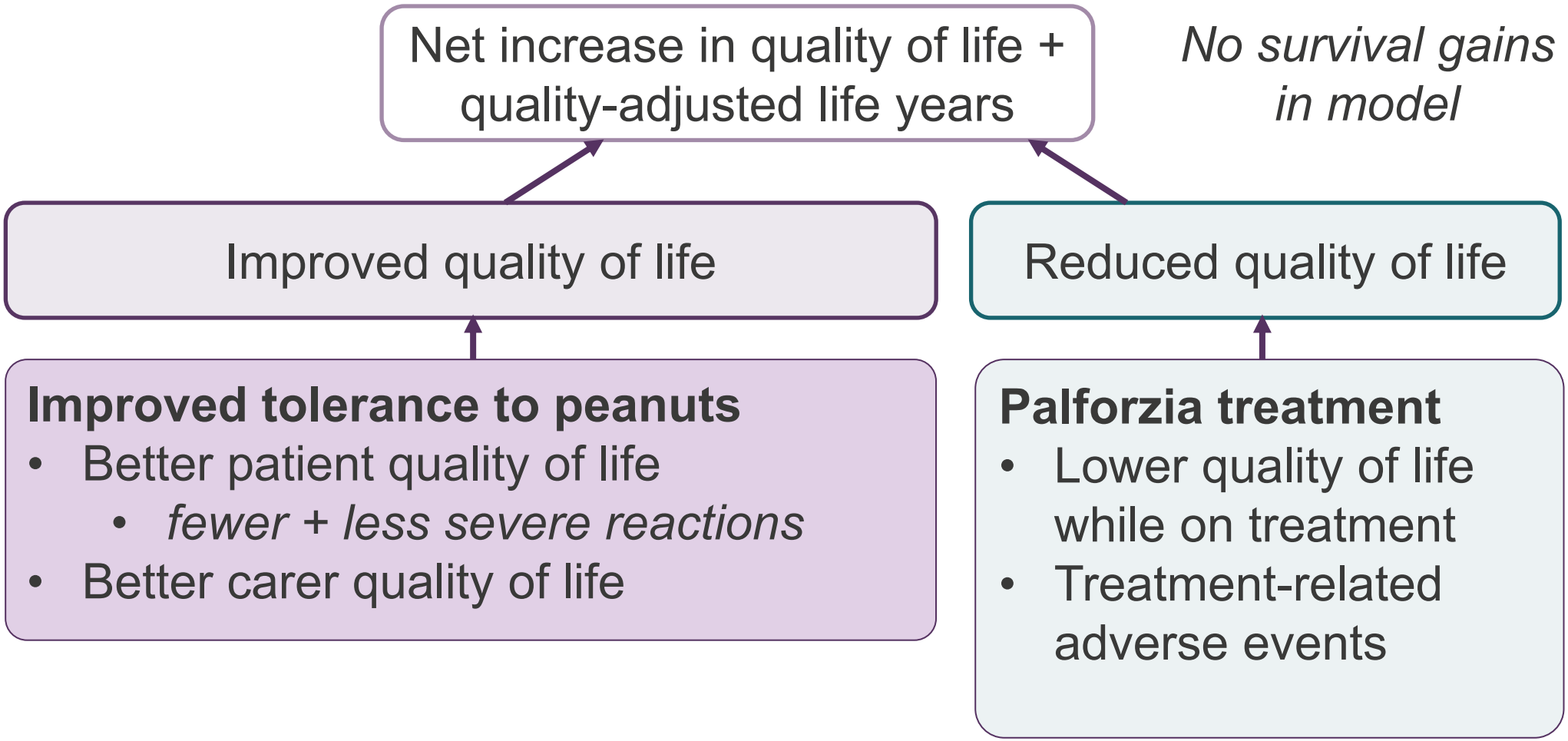
[a] PALISADE Group of Clinical Investigators. NEJM (2018) 22;379(21):1991-2001.

Cost effectiveness

Conceptual: how quality-adjusted life years accrue

Palforzia compared to avoiding peanuts; all gains via better quality of life including carers; company does not assume Palforzia prolongs life



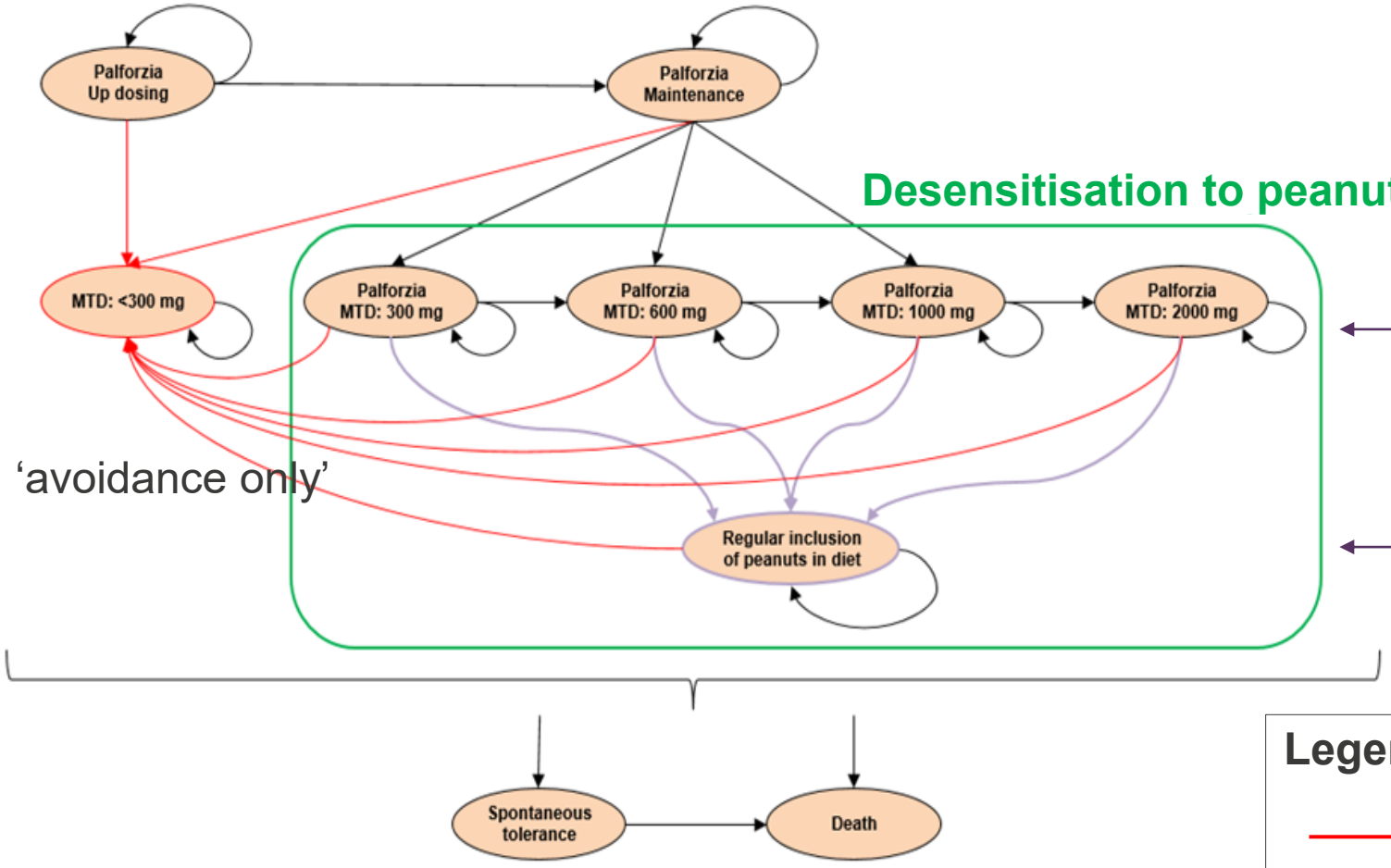
- *Is it reasonable to assume no risk of death linked to anaphylaxis?*
- *Is it reasonable to assume Palforzia has no effect on risk of dying?*

Company cost effectiveness model

Type	Markov cohort state transition model
Structure	5 phases: 1 initial dose escalation 2 up-dosing 3 maintenance 4 extension 5 extrapolation
Population	Children and adolescents under the care of a specialist
Intervention	Palforzia + avoiding peanuts
Comparator	Avoiding peanuts only
Time horizon	90 years (age at model entry: 10 years – mean age in PALISADE)
Model cycle	Up-dosing: 20 cycles of 14 days, until a maximum maintenance dose of 300 mg is achieved; maintenance: 8 cycles of 28 days
Discounting	3.5% per annum, costs and outcomes
Perspective	NHS England and Personal Social Services
Treatment duration	~2 years to lifetime: after ~2 years people can 1) stay on Palforzia lifelong; 2) switch to regularly including peanut in diet; or 3) return to avoiding peanuts
Spontaneous tolerance	5% children
Risk of death	2019 UK life tables general population; peanut allergy/Palforzia no effect on risk
Quality of life	*De-novo* study: adolescent self-reported (EQ-5D-Y) & carer proxy-reported (EQ-5D) + carer quality of life (EQ-5D)
Resources and costs	Costs of: drug and administration; food challenge test; routine monitoring; other; reactions to accidental exposure to peanut; treatment related adverse events

Model structure by treatment: based on PALISADE

Palforzia + avoiding peanuts; health states by amount tolerated



Transient events:

Reactions to accidental peanut exposure

- *Frequency and severity linked to health state only*

Adverse reactions

- *Frequency and severity linked to treatment received and health state*

Legend:

Stop Palforzia or include peanuts; move to 'avoidance only'

Stop Palforzia; move to 'peanuts in diet'

Abbreviations: MTD, maximum tolerated dose of peanut protein

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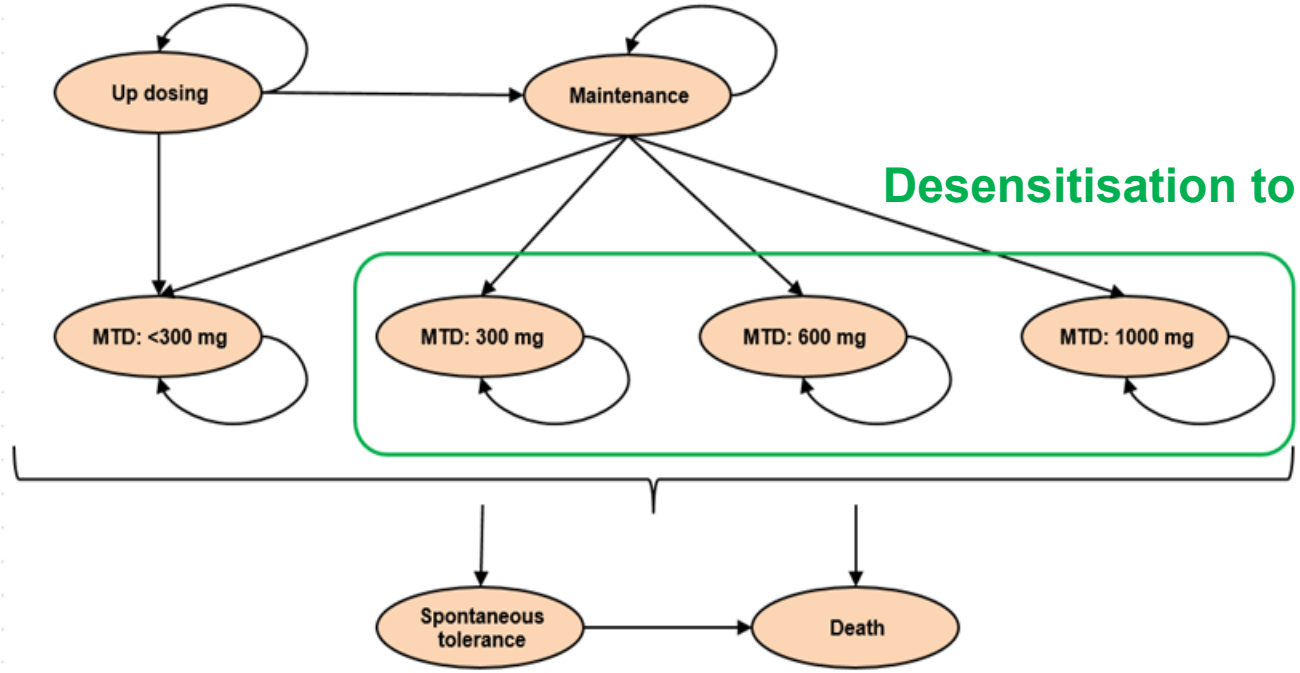
Model structure by treatment: based on PALISADE

Avoiding peanuts only; health states by amount tolerated



Desensitisation to peanuts

Transient events:

Reactions to accidental peanut exposure
- *Frequency and severity linked to health state*

Adverse reactions
- *Frequency and severity linked to treatment received and health state*

ERG – company model reasonable but some uncertainty related to:

- Multiple health states defined by tolerance reduce sample sizes informing how likely people are to move between health states → but give better face validity to quality of life gains
- Company did not include 'max tolerated dose: 2000 mg' health state for 'avoiding peanuts only'
- Company safety study – prolonged treatment and higher tolerance level leads to fewer treatment-related adverse events and accidental exposures

Abbreviations: MTD, maximum tolerated dose of peanut protein

Model structure: 4 main phases

Max duration (approx. duration)	20 cycles *14 days (6 months)	8 cycles *28 days (6 months)	1 cycle *224.5 days (7.5 months)	88 cycles *1 year (until end of model horizon)
Health states[a]	Up-dosing, MTD<300 mg	Maintenance, MTD<300 mg	MTD: <300, 300, 600, 1000 mg	MTD: <300, 300, 600, 1000, 2000 mg or 'including peanuts'
Transition probabilities	PALISADE, up-dosing	PALISADE, maintenance	Food challenge & PALISADE follow-on	Food challenge & clinical opinion
Reactions to accidental peanut exposure	PALISADE, up-dosing	PALISADE, maintenance	Risk reduction model based on PALISADE[b], per MTD health state	
Treatment-related adverse events[c]	PALISADE, up-dosing	PALISADE, maintenance	PALISADE follow-on, per MTD state[d]	
Quality of life Palforzia	Initial decrease from baseline	Some increase from baseline	Same as maintenance	Depends on MTD health state[d]
Quality of life 'avoidance'	Baseline quality of life throughout (equal to 'MTD<300 mg' state)			

MTD, maximum tolerated dose of peanut protein. Transition probabilities: probability of moving between different health states.
[a] Patients can stop treatment and move to 'MTD<300 mg', spontaneous tolerance or death from all health states; [b] using baseline and follow-up data from PALISADE; [c] No treatment-related anaphylactic reactions in the avoidance arm and 'MTD<300 mg'/avoidance state; [d] Rates for 'MTD: 2000 mg' and 'including peanuts' assumed equal to 'MTD: 1000 mg' state.

Source of effectiveness inputs to model

Outcome	Included in modelling? PALISADE	ARTEMIS	PALISADE follow-on	Other
Peanut allergy desensitisation	✓	✓[a]	✓	X
Frequency of accidental peanut exposure needing treatment	✓	✓[a]	X	X
Stopping treatment	✓	✓[a]	✓	X
Adverse events including anaphylaxis	✓	✓[a]	✓	X
Patient quality of life: • Food Allergy Independent Measure • Food Allergy-Related Quality of Life Questionnaire	 X X	 X X	 X X	 X X
• EQ-5D-Y – adolescent self-reported • EQ-5D – carer proxy-reported	X X	X X	X X	✓[b] ✓[b]
Carer quality of life – EQ-5D	X	X	X	✓[b]
Long term assumptions about % people: • including peanuts in diet after Palforzia • then switching back to peanut avoidance • with spontaneous tolerance	 X X X	 X X X	 X X X	 ✓[c] ✓[c] ✓[d]

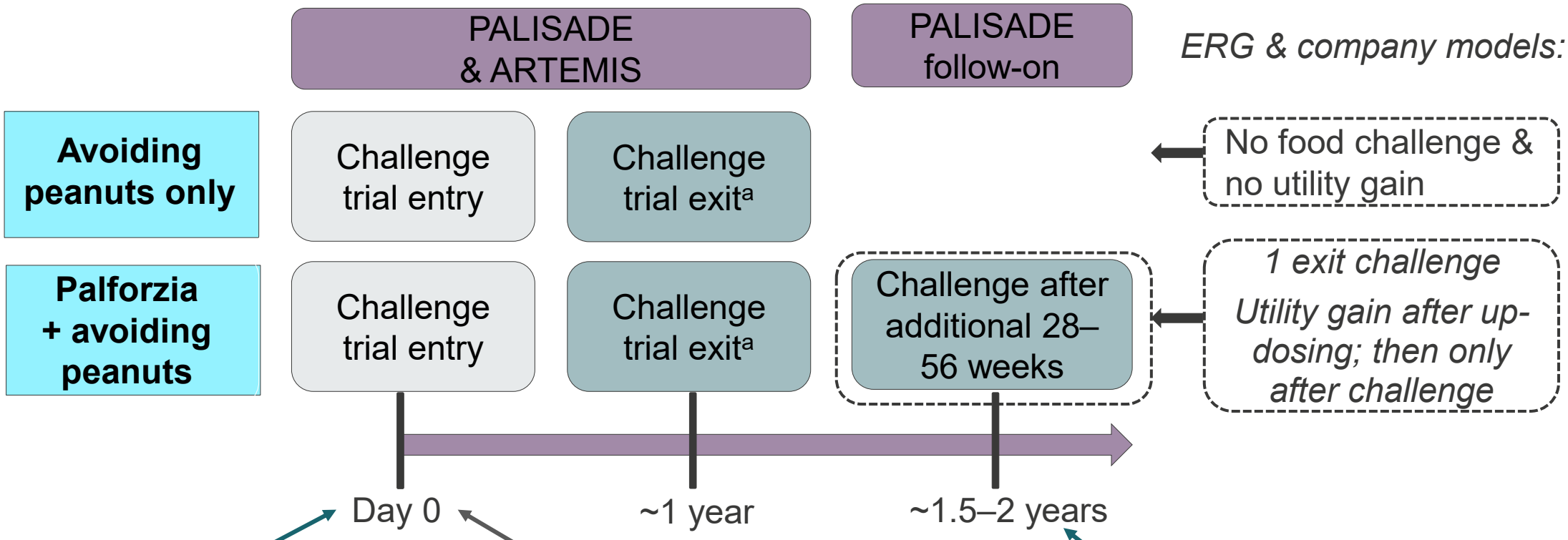
[a] Included in scenario analysis; [b] *de novo* utility study; [c] clinical opinion "SHELF"; [d] literature and clinical opinion

Company and ERG base cases

Assumption	Company and ERG agree?	Company	ERG
Timings of oral food challenge in clinical practice & gains in quality of life	✓	• **Palforzia + avoiding peanuts:** 1 food challenge at 2 years; treatment continues to 2 years; utility gains after ○ No screening food challenge • **Avoiding peanuts only**: no food challenges; no related utility gains	
Natural history for people who tolerate ≥300 mg peanut after 2 years of Palforzia	✓ but some concerns	• XXX continue treatment and have benefit lifelong • XXX start to include peanuts in diet ○ XXX of the XXX then switch back to avoiding peanuts	
Resource use and costs – anaphylactic reactions and adverse events	✓	• Included all treatment-related adverse events • Ambulance and A&E visit for all anaphylactic reactions • Cost of ambulance call out £257	
Utilities in children and adolescents	X	All adolescent self-reported **AND** carer proxy of patient; treatment-naïve & Palforzia-treated (N=157)	Treatment-naïve adolescent self-reported (N=38)
Utilities in carers	✓ but some concerns	Carer quality of life included (N=157 carers, XXXX carers per child)	

Timings of (food) challenge in clinical trials vs NHS practice

Company and EGR include 1 exit challenge only; affects quality of life gains



BSACI: 'strongly recommends' food challenge before treatment – to confirm allergy still present and severity

Not included in model

NICE technical team: modelled outcomes for sensitivity to <100 mg[b] peanut protein outcomes for all-comers may differ

Clinical experts: food challenges not used to determine desensitisation in NHS

Burden to NHS

Max 1 at 1-2 years but case for 'doing none'

BSACI: no need for 2nd challenge

- *What assumptions and costs relevant to NHS practice?*
- *If no exit food challenge in NHS practice, how should quality of life gains be modelled?*

BSACI, British Society for Allergy and Clinical Immunology; [a] end of maintenance treatment: after 12 months in PALISADE and after up to ~13 months in ARTEMIS; [b] company & ERG base cases (PALISADE); 300 mg in scenario analysis based on ARTMIS.

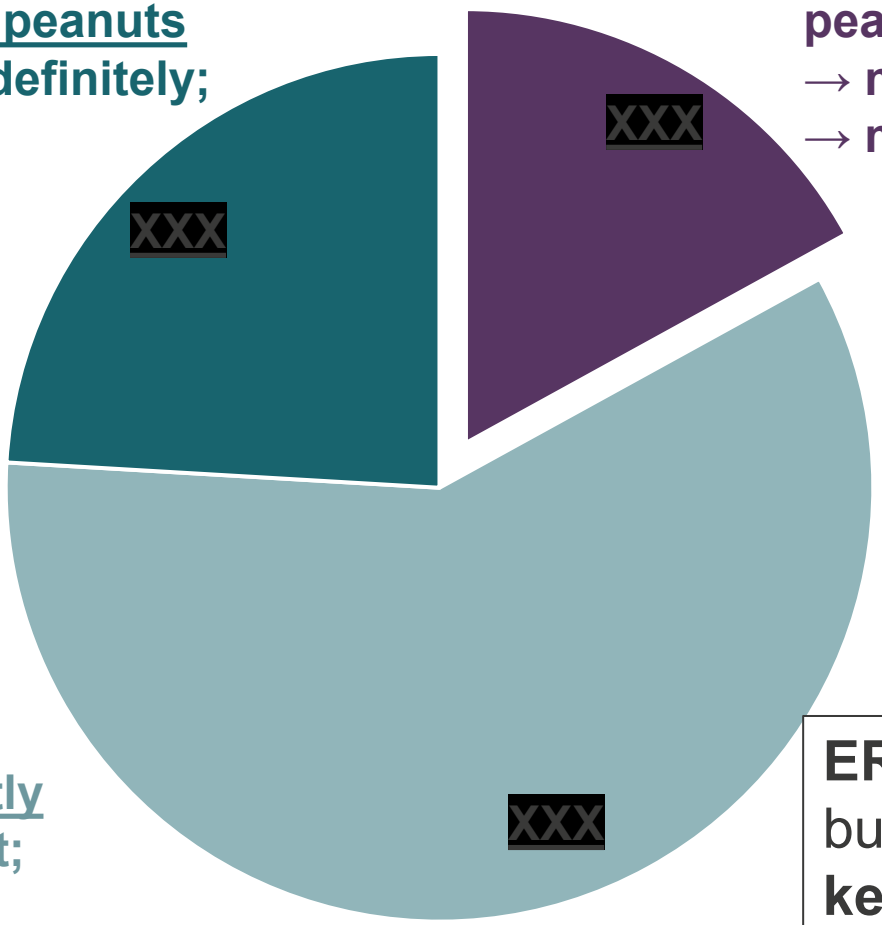
Company - treated natural history after 2 years Palforzia (1)

For people with tolerance to ≥300 mg in oral food challenge

Based on 'SHELF' expert elicitation – X clinical experts

Stop Palforzia, move to peanuts in diet, then move to avoiding peanuts
→ lose treatment benefit indefinitely;
→ no treatment costs

Continue Palforzia + avoid peanuts lifelong
→ maintain treatment benefit;
→ maintain treatment costs



Stop Palforzia, move to peanuts in diet permanently
→ maintain treatment benefit;
→ no treatment costs

ERG: estimates reasonable but **highly uncertain;** **key drivers** of cost-effectiveness estimates

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Does not include spontaneous tolerance or death

Treated natural history after 2 years of Palforzia (2)

Patient and clinical experts: use and benefits in clinical practice unclear

Patient experts:

- People who tolerate higher doses of peanuts more likely to include them in their diets
- People aged >17 years likely to switch to dietary peanuts to avoid 'being different from friends'
- People committed to 2 years' treatment motivated to maintain tolerance → likely to include peanuts in diet
- Psychological stress and anxiety of eating peanuts – diligently avoided, greatly feared

Clinical experts:

- Disagree that XXX would continue Palforzia indefinitely – expensive and not justified when peanuts in diet 'free'
- Most patient would start including peanuts after 2 years with or without food challenge → lower burden of treatment and clinic visits
- 10-30% may then stop eating peanuts; poor compliance linked to: taste aversion, low motivation, side effects, restrictions around meals and exercise, lack of support

British Society for Allergy and Clinical Immunology:

- Palforzia should be used only for initial up-dosing phase; people could start peanuts in diet when they reach tolerance to ½ peanut (100 mg) or 300 mg maintenance dose

◉ *Are model assumptions reasonable?*
◉ *What should model include for on-going treatment?*

Resource use and costs

Costs of resources, anaphylaxis, adverse events

Company and ERG agree

Company and ERG:

- Model all treatment-related adverse events that impact costs, benefits, even if rare
- Model ambulance and hospital visit for all anaphylactic reactions, regardless of severity or cause – in line with anaphylaxis guidelines
- Recalculated ambulance services costs (£257)

Clinical and patient experts:

- All patients with anaphylaxis should receive same care, regardless of cause
- Many patients not taken to hospital even after adrenaline – managed by paramedics
- Reactions to Palforzia expected – more likely to be treated promptly and be less severe; and have lower impact on patient quality of life than unexpected events
- People on Palforzia well trained to recognise anaphylaxis:
  - may use adrenaline earlier and have less severe event
  - more likely to call an ambulance

◉ *Are anaphylactic reactions and adverse events adequately modelled?*

Utilities

1. Adolescent self-reported versus carer proxy-reported data
2. Differences between treatment-naïve and Palforzia-treated data
3. Interview data versus online survey-reported data
4. Carer quality of life

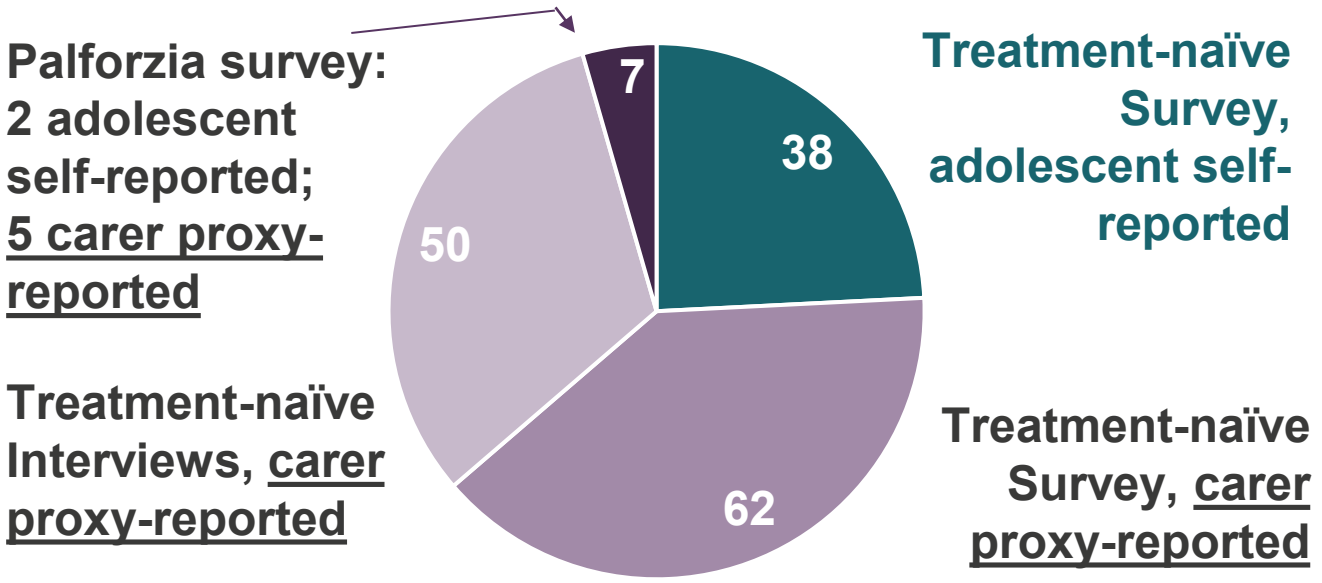
Utility values – background

Key driver. Company + ERG disagree on use of carer as proxy for child and including retrospective survey from Palforzia-treated patients

Company did *de novo* utility study – **pooled data (n=157)** from different sources

ERG prefers to only use data from **38 treatment-naïve self-reported** surveys

- Concerned that carer-proxy reporting may reflect impact on carers as well as children → risks double-counting as carer disutility also included
- Prefers self-reported EQ-5D-Y data, in line with NICE reference case, even if sample smaller
- Noted large differences between 2 approaches; key driver of cost-effectiveness



Utility values *Adolescent self-reported vs carer proxy-reported (1)*

Guide Methods Technology Appraisal 2013: When' not possible to obtain measurements of health-related quality of life directly from patients…should be obtained from person who acts as their carer'

Decision Support Unit (2019): HRQoL assessment in children and adolescents

- Challenging
- EQ-5D-Y child-friendly version of EQ-5D answerable by a parent or carer for aged 4–7 years and self-reported for aged 8–11 years; EQ-5D-Y or EQ-5D appropriate for age 12 and older

Company:

- [redacted]
- Where both self-reported and carer-reported data available, health state utility values similar:

Health-state	EQ-5D, mean (SE)	
	Adolescent self-reported N=38	Carer-proxy N=38
Baseline	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]
Δ from baseline	[redacted]	[redacted]

- Supported by FAQLQ data from PALISADE

ERG:

- Unclear whether this observation can be extrapolated to full sample – likely not considering large differences between company and ERG preferred utilities
- Unclear FAQLQ results can be extrapolated to EQ-5D-Y

NICE

FAQLQ, Food Allergy Quality of Life Questionnaire

Utility values *Adolescent self-reported vs carer proxy-reported (2)*

Patient experts:

- Carers may be more considerate than the child of QoL – adolescents may be more dismissive
- 4- to 11-year-olds not represented if carer responses excluded

Clinical experts:

- Children's self-reported and parental estimates of QoL differ:
  - Peanut allergy[1]
  - Allergic rhinitis[2] – parents underestimate benefit of treatment
- Parents shield many adolescents from impact of disease – adolescents may be less able to say how food allergy impacts their quality of life
- Parents take holistic, family-focussed and future-facing view; children focus on own world
- Improving carer's QoL will impact on child's QoL
- QoL likely to improve when have an allergic reaction under controlled circumstances[1]; 1/3 of the improvement in QoL with oral immunotherapy shown relates to entry food challenge[3]

◉ *Should model include carer proxy-reported utility data be included?*

QoL, quality of life. [1] Burrell et al. Arch. Dis. Child. 2021;106:558-563; [2] Berger el al. Pediatr Allergy Immunol 2016;27(2):126-33; [3] Patel et al, J. Allergy Clin Immunol. 2020.

Utility values *Differences between treatment-naïve and treated*

Company:	**ERG:**
• Uses all adolescent self-reported data, including 2 Palforzia-treated patients	• Disagrees: different methods used for 2 groups • Risk of recall bias in Palforzia-treated survey

Health state	EQ-5D utilities, mean (SE), adolescent self-reported		
	N=2 Palforzia-treated	N=38 treatment-naïve	N=40 pooled
Baseline quality of life	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]
Δ from baseline	[redacted]	[redacted]	[redacted]

Utilities plausible?

18-fold difference

Health state	EQ-5D utilities, mean (SE), pooled self- + proxy-reported		
	N=7 Palforzia-treated	N=150 treatment-naïve	N=157 pooled
Baseline quality of life	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]
Δ from baseline	[redacted]	[redacted]	[redacted]

4.3-fold difference

◉ *Do data from Palforzia-treated people have face-validity? Should model include them?*

SE, standard error

Utility values *Interview- versus online survey-reported data*

Company:

- [redacted]
- [redacted]
- [redacted]

ERG:

- In-person interviews may give more robust data than online surveys, but have limitations e.g. acquiescence bias
- Benefits of self-reported data outweigh limitations of online surveys

Health state	EQ-5D utilities, mean (SE)		
	Online survey (n=100[a])	Interviews (n=50[b])	Pooled (n=150)
Baseline quality of life	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts	[redacted]	[redacted]	[redacted]
Δ from baseline	[redacted]	[redacted]	[redacted]

[a] Pooled 38 adolescent self-reported + 62 carer-reported (all treatment-naïve);
[b] All 50 caregiver-reported (treatment-naïve).
SE, standard error

NICE

- *Appropriate to pool data collected using different methods?*
- *Which source is more reliable?*

Utility values *Carer quality of life*

Decision Support Unit (2019): carer disutility in minority of appraisals (4%; 16/422); most appraisals accept 1 carer only

NICE methods review (2021): evidence for 1º caregiver likely more robust than for other carers

Company:

- Model includes carer disutility to age 18 years – pooled data all sources
- Average [redacted] carers per patient

ERG

- NICE reference case: can consider 'direct' health effects on carers 'where relevant' – unclear if appropriate in peanut allergy but seems reasonable
- Number of carers uncertain – scenario with 1 carer

Health state	EQ-5D utilities							
	Treatment-naïve, survey (n=100)		Treatment-naïve, interviews (n=50)		Palforzia-treated survey (n=7)		All pooled (n=157)	
	Mean (SE)	Disutility	Mean (SE)	Disutility	Mean (SE)	Disutility	Mean (SE)	Disutility
Baseline quality of life	[redacted]							
Up-dosing	[redacted]							
Maintenance	[redacted]							
Tolerate 6-8 peanuts	[redacted]							

◉ *Should model include carer disutility? If so, using which source and how many carers?*

HRQoL, health-related quality of life; SE, standard error

Utility values *Comparison of all approaches*

Benefit of Palforzia higher in company base case & scenario

Health state	Mean EQ-5D utilities						
	Company base case	Company scenario	ERG base case	ERG scenarios			
	All data pooled (N=157)	Adolescent pooled (N=40)	Adolescent treatment-naïve (N=38)	Adolescent mixed[a] (N=38 / 40)	Adolescent + carer proxy pooled, treatment-naïve only		
					All (N=150)	Interviews (n=50)	Survey (n=100)
Baseline[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tolerate 6-8 peanuts[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Δ from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

◉ *Which approach to estimating utility values is most appropriate?*

SE, standard error. [a] ERG scenario analysis uses data from 38 respondents for current health, up-dosing and maintenance (recall biases is greatest); and pooled 40 respondents data for tolerance state of 6-8 peanuts (for the committee's information); [b] 'Entry' and 'MTD: <300 mg' states; [c] 'MTD: 2000 mg' and 'peanuts in diet' states

Recap: Company and ERG base cases

Recap: Company and ERG base cases

Assumption	Company and ERG agree?	Company	ERG
Timings of oral food challenge in clinical practice & gains in quality of life	✓	• **Palforzia + avoiding peanuts:** 1 food challenge at 2 years; treatment continues to 2 years; utility gains after ○ No screening food challenge • **Avoiding peanuts only**: no food challenges; no related utility gains	
Natural history for people who tolerate ≥300 mg peanut after 2 years of Palforzia	✓ but some concerns	• XXX continue treatment and have benefit lifelong • XXX start to include peanuts in diet ○ XXX of the XXX then switch back to avoiding peanuts	
Resource use and costs – anaphylactic reactions and adverse events	✓	• Included all treatment-related adverse events • Ambulance and A&E visit for all anaphylactic reactions • Cost of ambulance call out £257	
Utilities in children and adolescents	X	All adolescent self-reported **AND** carer proxy of patient; treatment-naïve & Palforzia-treated (N=157)	Treatment-naïve adolescent self-reported (N=38)
Utilities in carers	✓ but some concerns	Carer quality of life included (N=157 carers, XXXX carers per child)	

Cost effectiveness results

No patient access scheme, no comparator discounts

Company and ERG base cases

Pairwise deterministic + probabilistic: Palforzia[a] with avoiding peanuts vs avoiding peanuts only; small QALY differences

Base case	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case deterministic:					
Palforzia + avoid	33,769	20.05	20,458	0.86	23,745
Avoid only	12,285	19.14			
Company base case probabilistic:					
Palforzia + avoid	34,618	19.99	22,803	0.88	25,940
Avoid only	11,815	19.11			
ERG preferred base case deterministic:					
Palforzia + avoid	32,332	20.34	20,458	0.56	36,565
Avoid only	11,874	19.78			
ERG preferred base case probabilistic:					
Palforzia + avoid	34,537	20.35	22,738	0.57	39,716
Avoid only	11,799	19.78			

NICE

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

[a] At list price; no confidential discounts available

ERG scenarios: trial population, baseline food challenge and spontaneous tolerance

Palforzia + avoid peanuts vs avoid peanuts only; deterministic

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	20,458	0.86	23,745
ERG base case	20,458	0.56	36,565
ERG scenario: trial population (base case: PALISADE)			
ARTEMIS population	19,483	0.54	36,394
ERG scenario: screening food challenge (base case: not included)			
Include an additional food challenge prior to commencing Palforzia treatment[a]	20,734	0.56	37,059
ERG scenarios: spontaneous tolerance (base case: 5% lifetime rate)			
10% spontaneous tolerance	20,306	0.56	36,607
20% spontaneous tolerance	20,012	0.55	36,693

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG scenarios: long term assumptions

For people with ≥300 mg peanut tolerance after 2 years' Palforzia
Palforzia with avoiding peanuts vs avoiding peanuts only; deterministic

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	20,458	0.86	23,745
ERG preferred ICER	20,458	0.56	36,565
ERG scenarios: % starting peanuts in diet after Palforzia base case: XXXX			
Mean across all SHELF participants (XXX)	25,242	0.57	44,284
Low value (XXXXXXXXXXXXXXXXXXXX)	28,659	0.58	49,626
High value (XXXXXXXXXXXXXXXXXXXX)	14,991	0.55	27,381
ERG scenarios: % moving back from peanuts in diet to avoidance base case: XXX			
Low value (XXXXXXXXXXXXXXXXXXXX)	20,541	0.60	34,087
High value (XXXXXXXXXXXXXXXXXXXX)	20,351	0.50	40,386
ERG scenarios: % continuing Palforzia lifelong base case: XXXX			
0% - people redistributed equally to peanuts in diet and peanut avoidance[c]	8,840	0.53	16,555
0% - all redistributed to peanut avoidance[d]	8,668	0.45	19,494

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
[a] Rate based on consensus value reached between X experts included in SHELF elicitation;
[b] Palforzia: (XX%), peanuts in diet (XX%), avoidance (XX%)
[c] Palforzia (0%), peanuts in diet (XX%), avoidance (XX%)
[d] Palforzia (0%), peanuts in diet (XX%), avoidance (XX%)

NICE

Scenarios: alternative patient utility values

Palforzia + avoid peanuts vs avoid peanuts; deterministic

Technology	Source of utilities for patients	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	157 pooled self-reported and carer-reported responses	20,458	0.86	23,745
Company scenario	40 adolescent self-reported incl. 2 Palforzia-treated	20,458	0.94	21,713
ERG base case	38 adolescent self-reported, treatment-naive	20,458	0.56	36,565
ERG scenario #1	38 / 40 adolescent self-reported[a]	20,458	0.60	34,343
ERG scenario #2	150 treatment-naïve only (pooled self-reported and carer-reported)	20,458	0.74	27,735
ERG scenario #3	50 interviews only (treatment naïve; carer-reported responses)	20,458	0.87	23,562
ERG scenario #4	100 surveys only (treatment naïve; pooled self-reported and carer-reported responses)	20,458	0.67	30,756

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year;
[a] ERG scenario analysis uses data from 38 respondents for current health, up-dosing and maintenance (recall biases is greatest); and pooled 40 respondents' data for tolerance state of 6-8 peanuts (for the committee's information)

Scenarios: alternative carer utility values

Palforzia + avoid peanuts vs avoid peanuts; deterministic

Technology	Source of utilities for carers	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	All pooled data (N=157 carers); XXXX carers per child	20,458	0.86	23,745
ERG base case	All pooled data (N=157 carers); XXXX carers per child	20,458	0.56	36,565
ERG scenario #1	Treatment-naïve sample only (N=150 carers); XXXX carers per child	20,458	0.56	36,307
ERG scenario #2	Interview sample only (N=50 carers, all treatment naïve); XXXX carers per child	20,458	0.59	34,554
ERG scenario #3	Online survey sample only (N=100 carers, all treatment naïve); XXXX carers per child	20,458	0.55	37,382
ERG scenario #4	All pooled data (N=157 carers); 1 carer per child	20,458	0.50	40,789
ERG scenario #5	Remove carer disutility	20,458	0.43	47,119

NICE

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Innovation

Company considers Palforzia innovative:

- ***1st licensed immunotherapy***: *represents a potential step change*
- *1st oral immunotherapy that provides both a* ***standardised product*** *and a* ***structured dosing protocol*** *for desensitisation to peanut.*

Equalities

Variable access to specialist paediatric allergy services – may be linked to socioeconomic status

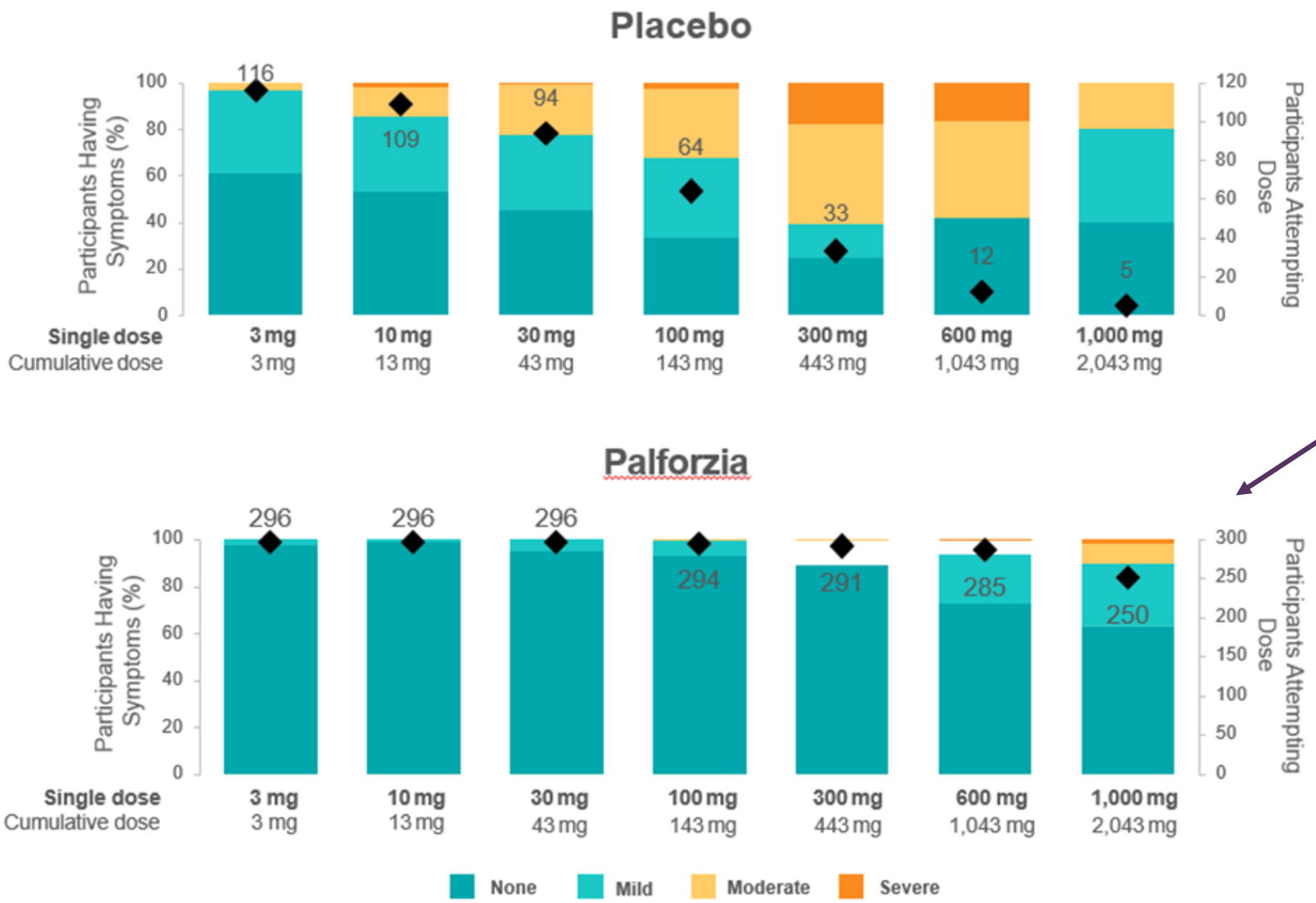
◉ *Is Palforzia a step-change in treatment? Benefits not captured in the modelling?*

◉ *Does Committee agree there are potential equalities issues?*

Supplementary slides

PALISADE – maximum severity of symptoms occurring during each dose of exit oral food challenge

Participants aged 4 to 17 years



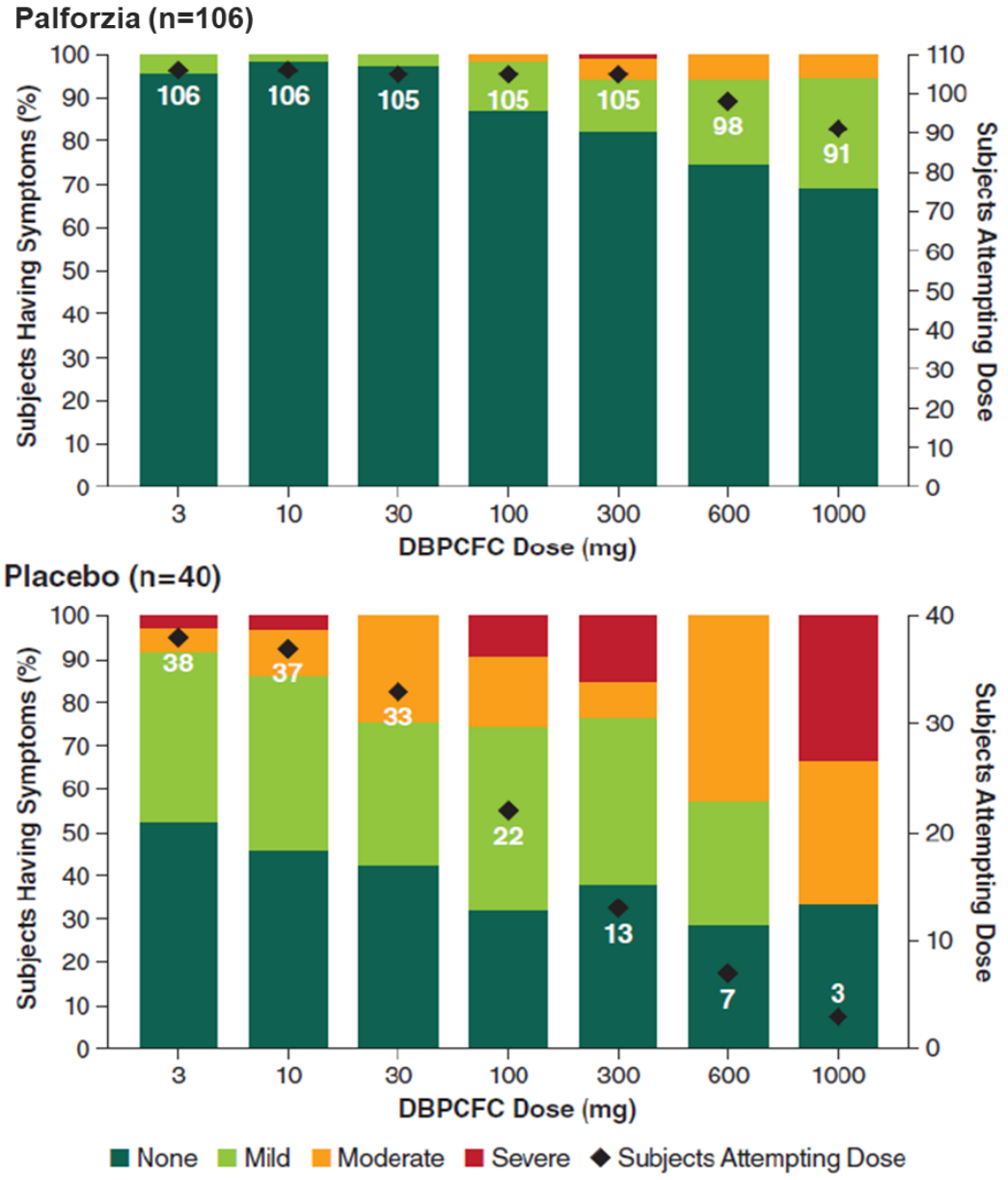
◆ Patients who continued ingesting sequential doses of peanut (n)

Most patients on Palforzia continued to ingest a high dose of peanut protein with no or mild symptoms

NICE

ARTEMIS – maximum severity of symptoms occurring during each dose of exit oral food challenge

Participants aged 4 to 17 years



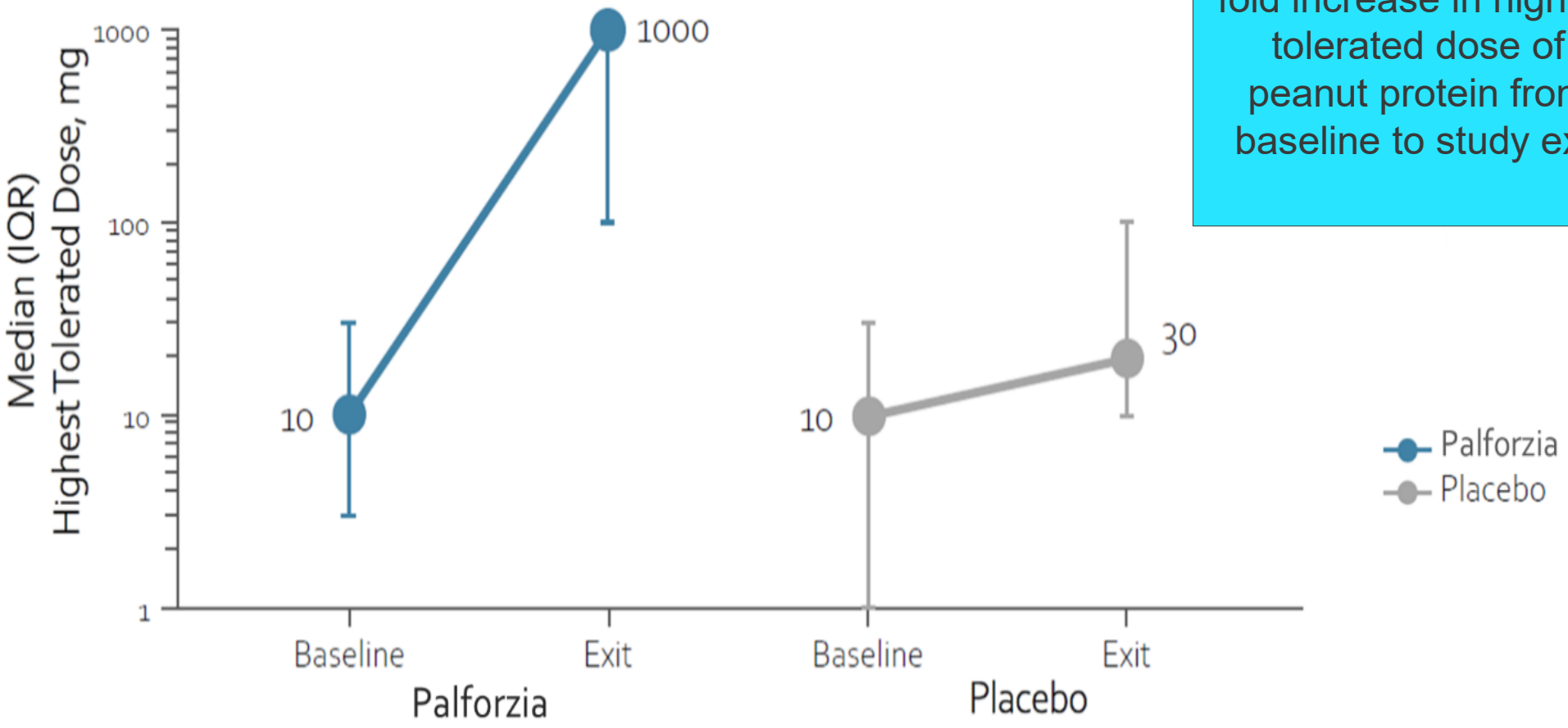
◆ Patients who continued ingesting sequential doses of peanut (n)

Most patients on Palforzia continued to ingest a high dose of peanut protein with no or mild symptoms

Highest tolerated dose at entry and exit oral food challenge (PALISADE and ARTEMIS)

Participants aged 4 to 17 years

Palforzia-treated participants had a 100-fold increase in highest tolerated dose of peanut protein from baseline to study exit



Modelling reactions to accidental peanut exposure

Frequency and severity linked to tolerance level

Company estimated:

- Mean baseline risk of accidental exposures needing treatment as XXX% per year, based on PALISADE baseline data and patient history.
- Relative risk reduction of XX% with tolerance to 300 mg and XX% with tolerance to 600 mg, 1000 mg peanut protein, based on data collected in PALISADE, per tolerance level in exit food challenge
- Relative risk reduction for tolerating 2000 mg assumed same as for 1000 mg peanut protein
- Combined weighted average annual risk per health state:

Accidental exposures to peanuts	Probability of reaction per year by health state (%)				
	<300 mg	300 mg	600 mg	1000 mg	2000 mg
Requiring any treatment	XXX	XXX	XXX	XXX	XXX
Requiring treatment with adrenaline	XXX	XXX	XXXX	XXXX	XXXX

ERG:

- Company approach seems reasonable but some uncertainty linked to assumption that distribution of daily accidental exposure is constant over time; small impact on cost-effectiveness estimates

◉ *Is company approach to model reactions to accidental peanut exposure reasonable?*

Modelling treatment-related adverse reactions

Frequency and severity linked to treatment received, model phase and health state

Company:

- Severity and frequency of treatment-related adverse events with Palforzia decrease with time → rates captured separately for up-dosing, maintenance and thereafter, for each health state
  - Based on PALISADE and PALISADE follow-on
  - Split into anaphylactic reactions, and other non-anaphylactic reactions
- Avoidance-only group: 0% treatment-related anaphylactic reactions

Palforzia-related adverse events	Probability per cycle (%)				
	300 mg	600 mg	1000 mg	2000 mg	Including peanuts
Mild anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe anaphylactic reactions[a]	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Moderate non-anaphylactic reactions[a]	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Severe non-anaphylactic reactions[a]	[redacted]	[redacted]	[redacted]	[redacted]	N/A

ERG:

- Company approach appropriate but informed by small number of events – uncertainty
- Including severe anaphylactic reactions and other non-anaphylactic reactions have minimal impact on cost-effectiveness estimates

◉ *Are treatment-related adverse reactions modelled appropriately?*

[a] Initial model excluded severe anaphylactic reactions and other non-anaphylactic reactions – included after technical engagement.
Abbreviations: N/A, not available (not provided)

Utility values for health states

Company response:	ERG critique:
• Utility gain in pooled data aligned with ICER-US model for peanut allergy (including Palforzia)	• Argument not relevant to NICE • Methods inconsistent between 2 models[a]
• Results from carer proxies are more aligned with other research suggesting that DALY burden from peanut allergy is greater than from uncomplicated type 1 diabetes	• Argument not robust: selective, narrow assessment of evidence • Likely possible to find alternative data or diseases to support use of different values

Base case utility values

- Key utility values used in for ‘desensitisation to peanuts’ and ‘peanuts in diet’:

	Company base case		ERG preferred	
Assumption / parameter	**Patient HSUV**	**Carer disutility**	**Patient HSUV**	**Carer disutility***
Maximum tolerated dose: 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Maximum tolerated dose: 600 mg	[redacted]	[redacted]	[redacted]	[redacted]
Maximum tolerated dose: 1000 mg	[redacted]	[redacted]	[redacted]	[redacted]
Maximum tolerated dose: 2000 mg	[redacted]	[redacted]	[redacted]	[redacted]
Peanuts in diet	[redacted]	[redacted]	[redacted]	[redacted]

◉: *Are these values reasonable?*